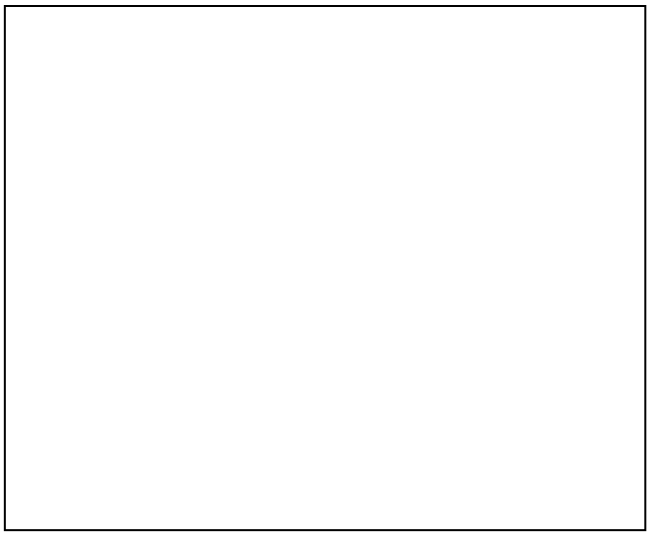
CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

June 18-19, 2003



Atlanta Marriott Century Center Hotel

Atlanta, Georgia

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MINUTES OF THE MEETING
June 18-19, 2003

JUNE 18, 2003

A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on June 18-19, 2003. The meeting agenda (posted on CDC's Website, http://www.cdc.gov/nip/) principally addressed the use of smallpox vaccine, but also addressed the influenza vaccine recommendation and the 2003 recommended childhood immunization and catch-up schedules. The meeting was convened by ACIP Chairmen Dr. John Modlin at 8:30 a.m.

Those present are listed on the attached sheets.

Opening Comments
ACIP Executive Secretary Dr. Dixie Snider announced that, upon CDC Director's Dr. Julie Gerberding had asked him to assume new duties. Since he could not continue to serve as ACIP's Executive Secretary, he had appointed Dr. John Livingood to serve as Acting Executive Secretary.

Certificates of appreciation were provided to ACIP members whose terms were about to expire on June 30: Dr. John Modlin (served since 10/5/95); Dr. Dennis Brooks (served since 10/2/99) and Dr. Lucy Tompkins (served since 9/7/99). A special token, an original oil painting, was given to Dr. Modlin for chairing the committee and for his work on complex issues with DHHS and CDC. Dr. Modlin commented that during his term, the recommendation on polio vaccine and hepatitis B vaccine was changed twice, recommendations were issued for three new vaccines, and the ACIP addressed the issues of thimerosal in vaccines and policies on anthrax and smallpox. He expressed his pleasure to serve with the committee members, staff, and Drs. Wharton and Orenstein, for whom he expressed immense respect.

The ACIP home page is www.CDC.gov/nip/acip; the email address is acip@cdc.gov. The last meeting of this year will be 10/15-16/03; the 2004 meeting dates will be on 2/24-25, 6/23-24, and 10/27-28/04. Public comment periods are scheduled during each meeting.

The ACIP charter provides that ex-officio members be asked to vote in the absence of quorum, and that the members state any conflicts of interest. Upon statements of such conflicts, the member would forego participation related to certain vaccine activities. However, since such work also enhances the members' activity while serving on the ACIP (e.g., serving on vaccine trial Data Safety Monitoring Boards – DSMB), the member can participate in discussions, but cannot vote on issues related to those vaccines. The following members stated such work

conflicts: Dr. Levin (clinical trials for Merck and SmithKline Beecham [SKB]); Dr. Poland (clinical trials for Merck); and Dr. Modlin (serves on Merck's DSMB).

After introductions, Dr. Modlin expressed the ACIP's sympathies to the family and colleagues of Dr. Victor Marchessault, who was the liaison of the Canadian Advisory Committee on Immunization, and who had recently died.

AGENDA

Influenza
Presenter: Dr. Keiji Fukuda

Overview: The ACIP influenza vaccination policy had been set in February 2003. This day's focus was on how a newly licensed live attenuated influenza vaccine (LAIV) may fit into that policy. FDA approved the licensure of MedImmune's LAIV, FluMist®, the first activated vaccine approved in the U.S. Dr. Fukuda summarized the history of ACIP recommendations on the use of influenza vaccine.

Update on 2003 Influenza Activity
Presenter: Ms. Lynette Brammer, Influenza Branch

- U.S.: In general Type A predominates (73% Type A/H1N1, 27% A/H3N2), but the predominating virus varyies by region.
- Europe: Types A and B; predominantly A/H3N2.
- Asia – A (H3N2).
- Southern Hemisphere: South America – predominantly Type A, with both H1 and H3 identified; South Africa – A/H3N2; little reported activity in Australia and New Zealand.
- Two instances of human infections with avian influenza viruses were reported, resulting in one death from Type A/H5N1 in Hong Kong. The Netherlands reported a case of H7/N7 as well as infections in pigs and humans. Bird infections were reported in Belgium and Germany. Of the 82 lab-confirmed infections, 8 had influenza-like illness (ILI). Person-to-person transmission was detected from 2 poultry workers to 3 family members and one death occurred. Details were provided and monitoring continues.
- The WHO and FDA's Virology and Related Biological Products Advisory Committee (VRBPAC) recommended retaining the 2002-03 vaccine components of A/New Caledonia/20/99-like (H1N1), A/Moscow/10/99-like (H3N2), A/Panama/2007/99, B/Hong Kong/330/01-like, B/Hong Kong/330/01, and B/Hong Kong/1434/02.
- CDC's recommendations for enhanced influenza surveillance include the continuation of year-round surveillance (laboratory and sentinel provider ILI surveillance), subtyping of all influenza A viruses, and the strengthening of some states' sentinel provider ILI surveillance.

Vaccine Supply Update
Presenter: Mr. Dennis O'Mara, NIP

The ACIP currently recommends that over 185 million persons receive influenza vaccine annually. This includes 83 million individuals with medical risk factors and 102 million others

such as medical care personnel, household contacts of those with medical risk factors, and healthy persons ages 50-64.

In contrast, vaccine production is projected etc., at 84.5 to 91 million doses for 2003. Although that is slightly less than the last two years, it is expected to surpass the 2002 actual usage. Of the three vaccine manufacturers, two produce inactivated vaccine and one, LAIV. On-time or early distribution is expected. The CMS payment rates increased to $7.72/dose for administration and ~$10/dose for the vaccine. A coordinated information campaign with the AMA and other partners/stakeholders is planned for providers and consumers to try to extend the vaccination campaign.

Discussion. Dr. Jim Young of MedImmune, reported an expected 4-6 million doses to be ready for the coming season. Mr. Philip Hosbach, of Aventis Pasteur (AvP) reported that ~45 million doses should be produced by November 1, 2003, similar to last year. The eggs will have to be ordered soon. If additional orders are not received soon, AvP will have to scale back or cease production. The Influenza Workgroup's >50 participating organizations expressed concern over the two-tiered influenza vaccination system. They asked the NIP, if the vaccine supply is adequate in August, to relax that system. Discussion of ACIP's opinion of this was tabled pending agenda time to discuss it.

MedImmune Presentation

Dr. Ed Connor, MedImmune's Director of Clinical Development, and representatives from their partner, Wyeth, discussed the development of FluMist®. FluMist® was developed to address the considerable morbidity (20-50 million annual infections) and mortality of influenza in the U.S.

FluMist® is a phenotypically and genotypically stable, cold-adapted, temperature-sensitive, attenuated influenza virus vaccine. It is built upon the attenuated strains derived from type A and type B donor viruses, with vaccine strains expressing contemporary hemagglutinin and neuraminidase antigens. On the previous day, FDA has approved its indication for active immunization to prevent influenza A and B virus diseases in healthy children and adolescents aged 5–17 years, and healthy adults aged 18 – 49 years.

The efficacy/effectiveness data for those aged 5-49 years, and the safety data and rationale for the indicated ages, were presented from efficacy/safety trials by Belshe et al, Treanor et al, Nichol et al, Kaiser/Black et al, and a Finnish daycare study by Vesikari et al.

Pivotal efficacy trial: Belshe et al. Two year field-randomized (2:1), double-blind, placebo-controlled trial among 1,602 healthy children aged 15-71 months at entry and 312 children aged 60-71 months, who received 1 or 2 doses in year 1 and a revaccination dose in year 2. Active surveillance was done with the primary endpoint, culture-confirmed influenza; circulating strains were A/Wuhan/359/95 (H3N2) and B/Beijing/184/93-like in Year 1; A/Sydney/05/97 (H3N2), a mismatched strain in Year 2. *Finding*: A high degree of efficacy (97.1%) was shown by reduction of attack rate of laboratory-confirmed illness, and effectiveness (31%) in a reduction in the attack rate of clinical illness parameters regardless of culture. Effectiveness (31%) was shown in each year and there was no relationship between timing of vaccination and

breakthrough cases. Outcomes for adults were any febrile illness. *Finding:* Effectiveness in reducing multiple illness measures was again clearly demonstrated.
Safety data supported the indication for the 5-49 year-old population. This was measured among 10,297 healthy children (1766 revaccinated) and 3297 healthy adults in several large placebo-controlled trials. Efficacy was shown in a 97% reduction in the attack rate of lab culture-confirmed influenza. A 31% reduction of all febrile illness was not statistically significant, but was statistically significant for all influenza-associated febrile illness.

Serious adverse events (SAE) were studied in placebo-controlled trials. The rate of SAEs was low and similar in the FluMist® and placebo groups. No SAEs were related to vaccine for either children or adults. Reactogenicity events were studied in children aged 60-71 months and showed small increases in mild URI symptoms after dose one. But fever rates were quite low and similar between the FluMist®/placebo groups for both doses one and two. For children getting annual vaccination, reactogenicity was lower in the second year than the first, an outcome paralleled among adults aged 18-49 years.

Medically attended events (MAE) were examined to assess FluMist's® safety among 10,000 Kaiser-enrolled children receiving two doses (aged <9 years) or one dose between ages 9-17 years. Database records of outcomes showed a statistically significant reduction of acute respiratory tract events, systemic bacterial infections and acute GI tract events, and rare events potentially related to influenza. Other evaluations were done for MAEs by setting, dose, and age group. Four MAEs were statistically increased (abdominal pain, enuresis, UTI, warts) and eleven MAEs significantly decreased (asthma/RAD, bronchitis, otitis media, ADD, etc.)

Overall conclusions for the indicated populations were of demonstrated efficacy in preventing culture-confirmed influenza in children and effectiveness in adults. FluMist®'s safety was established for healthy children aged 5 to 17 years and healthy adults aged 18-49. The rationale for the indicated 5-49 age was based on an open safety question in the Kaiser trial of children aged <5 years old and on limited data (~500 patients) for those aged 50-64 years. In particular, the Kaiser study of those aged <5 years showed a statistically significant increase in asthma/RAD that was not seen in those >5 years old.

Vaccine virus transmission has been studied for 30 years relative to the cold-adapted influenza vaccine (CAIV). Ten published studies of adults and children in various settings have not shown transmission associated with the CAIV. MedImmune conducted a randomized, double-blind, placebo-controlled study with FluMist® in a Finnish daycare center, of 197 children aged 8-36 months. To detect any vaccine virus transmission, extensive genotyping/phenotyping of nasal culture isolates were done on the first two days after a dose and at least three times weekly for 34 weeks. Eighty percent shed vaccine virus for a mean of 7.6 days. One child in the placebo group shed confirmed Type B vaccine virus at day 15 only. Four shed type A virus that could not be re-isolated for confirmation as either wild-type or vaccine virus. Wild-type A/H3N2 was circulating in the community

Findings: The risk of vaccine virus transmission was found to depend on age and intensity of contact. The Finnish day care study indicated a low chance of detecting transmission in the day

care setting (0.5% to 2.4%), and no phenotypic or genotypic reversion was observed in shed or transmitted viruses.

FluMist® indication: FluMist® is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents 5-17 years of age and healthy adults 18-49 years of age. FluMist® should not be used in individuals with underlying medical conditions that may predispose them to severe complications following *wild-type* influenza infection, or in individuals with a history of asthma or reactive airways disease. Its safety and efficacy is not established for persons with known/suspected immune deficiency, specific diseases and conditions associated with immunosuppressive treatment, or for persons unable to avoid close contact (e.g. household) with an immunocompromised host for at least 21 days after vaccination. The vaccine is stored frozen and thawed before it is administered intranasally in a dose of 0.5 ml (0.25 per nostril).

Summary: As an intranasal influenza vaccine for healthy individuals 5-49 years old, FluMist® may increase acceptance of influenza vaccine in healthy populations. It provides a safe and effective addition to the health care armamentarium for prevention of influenza, complements currently available vaccine, and permits earlier immunization of healthy individuals.

MedImmune's future evaluation plans include further Phase IV work, a large safety surveillance trial of 60,000 individuals over multiple seasons, and a shedding/immunogenicity trial among 300 persons. Expanded indications will also be studied for those aged 50-64, children <5 years old, and high risk populations.

FDA Presentation

Dr. ChrisAnna Mink, of the FDA's Center for Biologics Evaluation and Research (CBER), summarized their regulatory review for FluMist®'s licensure. This included the VRBPAC's review of the Biologics License Application (BLA). She outlined the latter for FluMist® from the initial submission in October 2000 through the June 17, 2003 approval.

The original requested indication, for use among those aged 1-64 years, was declined due to paucity of efficacy data in extreme age groups (<2 years and ≥50 years) and unresolved safety concerns (incomplete data, possible association with respiratory events, insufficient transmissibility data, no concurrent immunization data). In December 2002, MedImmune requested licensure for those aged ≥60 months to 64 years.

Data were reviewed in detail of the Northern California Kaiser safety trials, of FluMist® versus a placebo group, for outcomes of SAEs (result: 0.2% for both groups) or MAEs. There was no significant increase in the rates for the four pre-specified group diagnoses for FluMist® recipients for all ages, settings and doses combined (RR= 0.9, 90% CI). Another study was done to determine the relative risk of increased asthma events among 18-35 month-old subjects in all settings combined. An increased RR was found for asthma events for young children aged 12-59 months who received the vaccine. Of those, 8.5% had a history of asthma despite the exclusion criterion of parental report. However, there was no significant increase observed in RR for asthma for children aged >60 months.

Significant differences in *vaccination reactogenicity events* (RE) were seen between FluMist® and placebo groups for runny nose and low-grade fever for children and runny nose and sore throat for adults. The REs occurred commonly (> 60%) in both treatment groups in children and adults. No data for REs were solicited for 7–17 year olds. There were no apparent differences in RE rates by age group <50 years and 50–64 years of age. Most safety data were generated in healthy subjects.

A December 2002 assessment of all 20 trials resolved some of VRBPAC's concerns. It showed no increase in pneumonia, bronchitis or bronchiolitis events, and among rare events potentially related to wild type influenza, it showed no increase in seizures or reported cases of encephalitis, encephalopathy, Guillain-Barre Syndrome, or Reye's Syndrome.

In 2002, VRBPAC raised additional concerns: 1) the need for safety or efficacy data on concurrent immunization in any age group and for possible concurrent vaccinations of DTaP, MMR, and IPV for those aged 5-6 years, and pneumococcal vaccine for adults; and 2) transmissibility of the vaccine virus, since it was shed in 80% of young vaccinees aged 6–36 months and transmission was documented for one Type B and possibly four Type A's (estimated rate of 2.4%, 95% CI). *Safety concerns* included: 1) the small number (641) of subjects aged ≥50 years; 2) common reports of the solicited REs; 3) limited data on revaccination; and 4) the elevated RR of asthma events in children aged 12-59 months, although not above that age; frequency of vaccine virus strain shedding as well as transmission (but at an unclear rate).

In 2002, VRBPAC found efficacy demonstrated in year one for pediatric use against culture-confirmed influenza illness due to A/H3N2; for B after one or two doses in healthy children aged 15 to 72 months and after revaccination in Year 2; and for a subgroup of children aged 60-72 months. No field efficacy data were available for influenza A/H1N1. But while pediatric efficacy was demonstrated for those aged 60 – 84 months, efficacy for those aged 9–17 years had to be extrapolated. Effectiveness for adults aged 18–49 years was demonstrated for some endpoints, but not for adults aged 50-64 years.

So, VRBPAC posed questions to MedImmune about the adequacy of safety data for: healthy individuals aged 5–17 years, 18–49 years, and 50–64 years of age, particularly related to respiratory events (e.g. asthma and URI), shedding and transmission of vaccine strains after receipt of FluMist®, and annual revaccination. If those data were not adequate for specific age groups or if there were other safety concerns, MedImmune was asked to discuss what additional data should be requested. The same request for data, in hand or needed, was made for efficacy and effectiveness for the same age groups.

Upon a vote of VRBPAC's 18 voting members in 2002, the safety and efficacy/effectiveness data were accepted to allow licensure for use in healthy individuals aged 5-17 and 18-49, but not for those aged 50-64 years (10 voted yes, 8 no).

MedImmune was also asked: 1) to comment on the design and endpoints for the clinical study performed in adults for the release of new strains; and 2) to conduct clinical trials in adults for all new master virus seed (MVS). If the data were adequate to support safety and efficacy, MedImmune was asked to discuss what additional information, if any, should be requested from

post-marketing studies. MedImmune has committed to perform post-marketing studies, including a large safety trial and an evaluation of vaccine virus shedding in the 5-49 year age group.
So, the approved label indication for FluMist® is for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents aged 5-17 years and healthy adults 18 - 49 years of age. The schedule is a two-dose regimen (60 days, ±14 days apart) for the first use among children aged 5-8 years, and one dose for individuals aged 9-49 years.

Discussion included:

- There were no hospitalizations; 16 of 16 asthma events were treated with beta agonists, and most also with steroids. Of those children with RAD, 23% were on oral Prednisone,® 18.6% were on inhaled steroids, and 80% were on any beta agonist or steroid. But only 3% of the wheezing/short breath group were on oral prednisone, 9.4% on inhaled steroids, and 80% were given a beta agonist or steroid. There was no temporal distribution of the events related to vaccination within the first 42 days post-vaccination. About half of patients were not actively wheezing at that time, but a few adjustments in medication were necessary.
- Most of these patients had mild persistent or intermittent asthma and were treated intermittently. In the first Kaiser analysis, 8.8% of the population had a prior database hit for asthma/RAD and another 7% were detected in the 1995 database, for a total of 15% of the population. Wheezing was not identified as asthma or as an exclusion criteria.
- *Did any immunized children develop asthma who had no history of asthma?* Some of those cases had a prior history in the database; some had codes that might indicate asthma. In terms of a larger encashment, for wheezing, the 1.58 RR was not statistically significant, but there is still an open question about an increased risk. But of the 16 FluMist® recipients aged 18-35 months, 7 had a history of asthma/wheezing upon medical chart history; 9 did not.
- Seven of the 20,000 FluMist® recipients were pregnant at the time; six delivered healthy children and one had a therapeutic abortion. Of six participants who became pregnant during the follow-up period, three had healthy babies, one was premature (32 weeks) and there was one spontaneous abortion (in the placebo group). There were no congenital anomalies. Dr. Gall recommended doing pilot studies in pregnancy to explore this in a larger cohort. Although FluMist® is not indicated for those pregnant, that use will occur.
- The Workgroup found that older data on the bivalent vaccine suggesting a decreased efficacy when administered with DTP, presumably due to a febrile response to DTP. There are only two studies (Ruth Karron, *JIDl,* 1995 and Mary Lou Clements *JID*, 1996) to inform the use of a concurrent vaccine with a monovalent H1N1 and the identical H1N1 6/2 reassortant. Karront et al looked at 10^5 and 10^6 tcid50 doses of the monovalent cold-adapted compared to stand-alone monovalent vaccine given with DTP and OPV. The combined vaccine group had a reduced serum HAI response to influenza at the 10^6 compared to the stand-alone monovalent. The study was confounded by age, but the follow-on Clements study tested a 10^7 dose with the same vaccine as well as a second dose. Neither showed any interference with whole cell DTP, Hib, or OPV. MedImmune recommends two doses in children aged <9 years; in those studies, all those children were aged <6 months.

- In adults >65 years, 87% self-administered FluMist® or a placebo, not knowing what it was, the same day they got the inactivated vaccine. In the Nichol large effectiveness trial, 70% self-administered under observation by study staff and 30% asked to have it administered.
- *Was the Swiss-demonstrated association with Bell's Palsy examined?* There was none seen in our trials. The Swiss trial used a different product intranasal influenza vaccine, and the Bell's palsy was attributed to its adjuvant's *E. coli* labile toxin.
- *There are data showing synergy between live and inactivated vaccines in healthy individuals aged >65. Will that be pursued?* Treanor et al showed a 60% increased protection in adults aged >60 years when two vaccines were co-administered as opposed to TIV alone. But another recent trial of coadministered vaccines to individuals with COPD, versus inactivated vaccine alone, produced no statistically significant difference. However, the flu virus that year was well covered by the vaccine.

Implications of FluMist® to the NIP
Presenter: Mr. Dean Mason, NIP

MedImmune will manufacture FluMist®, but will co-market it with Wyeth Vaccines. It is the first U.S.-licensed intranasally administered influenza vaccine. The production target for the 2003-2004 season is 4 to 6 million doses. Wyeth will ship all product directly to the health care provider in 10x1 dose boxes with pre-filled 0.5 ml sprayers. It must be shipped and stored in a frozen state (5°F [-15°C] or colder). The price range may be $45-$50 per dose. In year one, few health insurance policies will offer coverage; most purchases will be "out-of-pocket" costs to the consumer.

- *FluMist® advantages* include its needle-less delivery and provision of an immunization choice to both the provider and consumer, and the industry has committed to vaccine production that will ensure an adequate supply.
- *Challenges.* However, FluMist® targets a population group for whom routine influenza vaccination has not been specifically recommended, and it faces limited VFC coverage (only for children aged 5-18, healthy, and the close contacts of persons in groups with defined risks who are not immune compromised). FluMist®'s need to be kept frozen poses problems to shipping and storage. Alternative and cheaper influenza vaccines are available, and if price differences are substantial, it will be difficult to negotiate public health contracts. That will also post funding issues for state and local budgets.

VFC coverage depends on FDA licensure (accomplished); the vaccine's inclusion in ACIP General Recommendations and supplemental recommendation; an ACIP vote for VFC coverage, CDC approval of ACIP's recommendation, and negotiation of a contract with the vaccine manufacturer. Other important steps are CDC's publication of the ACIP recommendations in the *MMWR*, after which state Medicaid programs have 90 days to incorporate the vaccine into their VFC coverage. But state health departments make policy decisions about vaccine purchase and supply. It also is important to remember that a general ACIP recommendation does not automatically confer VFC coverage, nor is VFC coverage appropriate for every vaccine for which there is an ACIP general recommendation (e.g., rabies, yellow fever vaccine).

Discussion included:

- As with any vaccine, FluMist®'s use is contraindicated for those with an allergy to any vaccine component. This is made in eggs. The only difference between this vaccine and one that is injectable is that this has no preservative but for aminoglycoside, but that is used very early upstream and is not detectable in the end product.
- Dr. Orenstein noted the importance to the NIP, programmatically, for the ACIP to indicate any preference for this versus the inactivated vaccine, and what is a recommendation versus a permissive use.
- *What is the stability when stored in a frost-free freezer?* It can be stored in a manual-defrost vaccine or a normal household freezer with automatically cycling defrost, as long as the temperature is maintained at -15°C. *That is similar only to the normal temperature requirements of varicella, so it involves a learning curve, and the second dose for younger children would fall in the part of the calendar year when getting them back in for second visit is hard.* The injector is calibrated to only inject 0.25 ml per nostril and includes a dose divider. The label will state a 60-day interval, but there is a ± 14 days window for the second dose.
- Simon Luce and Robert Belshe both published a cost effectiveness analysis of the vaccine in *Pediatrics* a few years ago, with assumptions similar to that for the inactivated influenza vaccine. It produced a $4 costs savings if the child has to be taken for an office visit to get dosed, and a ~$20 costs savings if done at an evening clinic.

Supplemental Recommendations for the Use of LAIV
Presenter: Dr. Scott Harper, NCID

A draft proposal of an ACIP supplemental guideline for the use of LAIV was presented. The questions and options raised in the Influenza Workgroup teleconferences about the guideline were as follow:

Document title: "Guidelines" or "Recommendations" for use of FluMist®?

Concurrent administration with other vaccines: Two options were offered, 1) not to administer concurrently with other live vaccines, or 2) not to do so with other live or inactivated vaccines.

LAIV use contraindications:
- Among poultry and swine workers: not to be used at all, or only not during outbreaks of animal influenza (page 8)?
- Household/close contacts: Three options offered had similar concepts but different emphases: 1) not used among household/close contacts of immunosuppressed persons; or 2) not so used "unless it is feasible to avoid contact with these persons for at least three weeks after receiving the vaccine"; or 3) not so used unless should contact is avoided with these persons for at least three weeks after receiving the vaccine"
- Use among healthcare workers, not specifically addressed: all healthcare workers, or only those dealing with immunosuppressed patients?
- "LAIV is available as an option for vaccination of healthy persons aged 5- 49 years, including persons in close contact with high risk groups and those wishing to avoid influenza. (See Tables 1 and 2.) Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response, its ease of administration, and the acceptability of an intranasal rather than intramuscular route of administration. (1)"

Timing of the LAIV administration: language similar to the yearly ACIP recommendation on influenza vaccination: optimally, October and November. But also, "children aged 5-8 years receiving LAIV for the first time should begin in October because those persons need a booster dose 6-10 weeks after the initial dose."

- Timing of the LAIV schedule: two options for children aged 5-8 years previously vaccinated with LAIV or TIV: 1) no booster dose required; or 2) only one dose of LAIV for children aged 5-8 previously immunized with it, but 2 doses of LAIV separated by 6-10 weeks for children aged 5-8 vaccinated only with TIV.

Discussion included:
Dr. Zimmerman, the Acting Chair of the Influenza Workgroup, and the only ACIP member in these discussions, reported on the latter to contribute to the ACIP's discussion.

1. The current recommendations on use of inactivated vaccine do not cite those aged 5-49 as a target group. They are only so if they are a household contact of a high risk person or a healthcare worker. Should it be recommended to stress those at high risk, or is this a guideline for a vaccine that is not targeted? Considerations include a real risk of transmission of vaccine virus from a vaccinee to a person with COPD or CHF and exacerbating their disease. But on the other hand, there is a low compliance rate for inactivated vaccine among household contacts of persons at high risk, and a person developing influenza itself can transmit it. The workgroup reached no consensus on this; he favored a guideline.

Discussion. This could be too subtle. It could be better to keep with recommendations and provide something explicit text on these points. But a "recommendation" could indicate an ACIP preference, something normally avoided. The discussion was TABLED until the committee first decided what it wanted to say about FluMist®, then determine it as a guideline or recommendation. In past, the ACIP stated the high risk groups who should receive influenza vaccine, and others wanting to reduce the risk of influenza and its complications could be vaccinated. The ACIP could state that those not at high risk (individuals, employers, and potentially society) could benefit from receiving the vaccination, and this vaccine provides one option. *A positive statement to this effect should be included*.

2. Administer with other vaccines: There has been a clear consensus to not give the LAIV within one month of live viral vaccines.

Discussion. ACIP's General Recommendations allow concurrent administration of live and inactivated vaccines. But in this case there is an incomplete safety data set; this would be a different ACIP recommendation. The FDA did not allow the package insert to advise concurrent administration, but only due to lack of data, not that data indicated against it. There are no serology data for other antigens in concurrent administration of the vaccine. Dr. Modlin commented that situations such as this one ACIP option is to differ from the package insert text. Dr. Abramson stated that the AAP would favor Option 1 due to concern about breaking with General Recommendations and increasingly confusing general practitioners. Although they do allow concurrent use of MMR and VZV, they would not favor Option 2. He proposed a third option, to stay with the General Recommendations allowance of concurrent vaccination.

It was agreed to say that, in general, it is permissible to give two vaccines together, but in this case, there are no data to indicate whether that should or should not be done. The clear consensus of ACIP was to be as consistent as possible with the General Recommendations.

3. Use of LAIV in poultry and swine workers. There is a theoretical possibility of recombination of an avian virus and the master donor strain to introduce a new virus into a completely naive population. Should this be a contraindication for these workers, or a precaution; or the latter only during outbreaks of animal influenza; or an advisory that this is a theoretical possibility?

Discussion. Dr. Coalingh, of MedImmune, said that the possibility of reassortment in a dually infected person or animal is well documented. The transmission can go either way, but the master viruses are temperature sensitive (39° for type A and 37° for type B). Hogs' body temperature is 39.5° and chickens are 42°, so the vaccine transmission risk is unlikely from human to animal transmission. But transmission the other way has not been discussed with FDA. Dr. Peter Paradiso, of Wyeth, stated that the vaccine hemaggutinins will be similar to those circulating in the wild strain, so the potential for transmission is similar to influenza transmission in the general population. He preferred to protect against wild influenza infection in that population than not. Dr. Mendelman added that an H5, H7, or H9 joining the master virus exchange would be attenuated.

There was consensus by the ACIP to not address this at all, since it was felt to be beyond the committee's purview.

4. Household members and close contacts of immunosuppressed persons: three options were offered.

Discussion included:

- In the Finnish study, the symptoms of the child with Type B, to whom the vaccine virus was transmitted, paralleled those of the placebo group.
- Since data indicate that transmission is very rare, follow-up after the vaccine's introduction and for later reconsideration is wise. But the risk precludes LAIV use in healthcare workers and perhaps many other adult healthy persons, since they have frequent contacts with immunocompromised persons. On the other hand, the likelihood of transmission among adults should not be higher than that of children in day care and both historical and FluMist® data support that adults shed virus for fewer days than do children.
- Option 2 is closest to the label and is applicable to household/close contacts; healthcare workers could be addressed separately. The post-marketing studies in 5-49 year-olds will demonstrate the shedding rate, not now known.
- For the immunocompromised patient, state that there is an alternative vaccine to prevent influenza.
- Dr. Neal Halsey noted this discussion's similarity to the debates when the varicella vaccine was licensed, with a similar desire to protect the household contacts. The coverage rate among those who should be protected is still low. He advised copying the language used for varicella: the vaccine is encouraged/recommended; if a rash develops, minimize contact. Being too conservative will preclude many families from getting the vaccine who should do so. Do not include household members as contraindicated persons and provide the

information on low risk of transmission, and presence of attenuated virus, and the data on influenza infection in the immunocompromised.

- There was agreement to this suggestion. There are treatment options for those who may develop disease. The availability of another vaccine can be stated, similar to the strategy used during the IPV/OPV transition.
- *How stable or subject to mutation is the cold-adapted vaccine?* It is stable. The Finnish trial allowed the last specimen to mutate as much as possible. No characteristics changed and the level of genetic stability was what would be expected for influenza. What changes occurred were not in the phenotypic locus and the transmission recipient's symptoms were not clinically different. There is also some information on the likelihood of recombination, if transmitted again, from early studies by Murphy and Clements. Wild-type viruses were added back to the Master Donor vaccine strain, producing complete to lesser attenuation among animals and humans. But again, a strain more virulent than wild-type was never seen.
- Dr. Livingood suggested an Option 3, where the inactivated vaccine is recommended or preferred for household contacts of immunosuppressed persons. Based on theoretical concerns, those vaccinated close contacts of immunosuppressed person should avoid contact for three weeks, or a specified time.
- Inserting any such language will be interpreted as an invitation to avoid the vaccine. If this is not a contraindication (it is only precaution on the package insert, as well), remove the 3-week text, which infers a preference for inactivated vaccine. Just state a preference for the inactivated vaccine and state that there is no data on whether household contacts can transmit this virus. Extensive details of those who should avoid vaccination will affect many healthcare workers who are still inadequately covered and this is an attenuated virus with a low rate of transmissibility.

It was agreed to insert that LAIV can be used in household contacts, however, because of..(cite concerns) inactivated vaccine is preferred in this situation." That will clearly convey that this can be used in these settings.

5. Use among healthcare workers may be acceptable in general settings, but what about settings with those who are immunosuppressed such as bone marrow transplant patients?

Discussion included:

- There are immunosuppressed people all over hospitals and in clinics and private practices. LAIV should not be used among healthcare workers until data support that use. They may be exposed to wild influenza virus anyway, but nuancing among healthcare workers is difficult if not impossible. The likelihood of hospitals wary of their bottom line investing $50/dose is also questionable.
- However, permissiveness among adults is desirable and 15% of healthcare workers are afraid of needles and therefore will not be vaccinated and they need to be so. The morbidity and mortality to patients cared for by unvaccinated healthcare workers is measurable.
- At the least, ACIP should restate the need to immunize healthcare workers. Consistency is also desirable and is lost if vaccine use is allowed in the same household and prolonged intimate contacts but not allowed elsewhere. Household contacts and healthcare workers need to be addressed with the same language.

- If healthcare workers are precluded, they will not be able to get the vaccine. Dr. Tompkins suggested saying "strongly recommended that all healthcare worker receive vaccination. The inactivated vaccine is preferred, but the LAIV is an acceptable option." However, "acceptable" implies that ACIP endorses it as not a risk, something not known. As an evidence-based guideline, the lack of evidence must be stated.
- It is not known how often the vaccine virus is transmitted or how it performs if transmitted. Small studies were cited indicating that shedding patterns were similar between HIV-infected and non-infected persons, and an NIH study in pediatric HIV-infected and non-infected people also showed the same safety profile and reactogenicity events.
- Dr. Steven Foster, of the American Pharmacists Association, asked if the 15% of healthcare workers who do not get a shot risk transmission by administering the vaccine. Dr. Modlin found that an interesting issue not yet addressed, but tabled that to check for some consensus.

The ACIP was in consensus to point out the absence of data and the theoretical risk and, in view of the ACIP's desire to be consistent with what was already suggested for household contacts, to indicate a preference for the alternative inactivated vaccine and the desirability to have healthcare workers vaccinated.

6. *Do children with one dose of inactivated vaccine need two doses of activated vaccine?*
   MedImmune's crossover trials had few children who received TIV in a prior year, but the safety trials did not preclude them. FDA noted no data on TIV followed by LAIV, but MedImmune presented epidemiological data, as well as Dr. Neuzil's serosusceptibility data, demonstrating that as children mature to age 6 years they become more seropositive with age. The break point is unknown, but MedImmune gave two doses the first season and a single dose thereafter to seronegative children. Children aged 60-79 months showed 100% efficacy for a single dose, versus 89% for 15-71 months in the study population as a whole. However, there are no data on TIV given a year before the by LAIV. Dr. Zimmerman preferred to consider the TIV a priming dose and to recommend only one dose of the LAIV. Dr. Foster commented that that would be easier to implement, but there are no data to support this. Dr. Glezen cited longitudinal studies' finding that most important was whether the child had an opportunity for exposure to natural infection. By age five today, they have been infected by all three types; they are already primed.

   The Halloran/Longini article in August's American *Journal of Epidemiology* found that a single dose of FluMist® was effective in children aged <5 who could not have been exposed to H1N1, since there has been no epidemic since 1996. The Belshe pediatric efficacy trial used a 2-dose regimen and a small group had one dose. The latter demonstrated efficacy, but that group had a small N and the lower bound of efficacy was 47%. Earlier data, also collected in this trial, looked at immunogenicity after 1 and then 2 doses. There was adequate response by one dose to H3N2 and B but not to H1N1; the latter emerged after dose two. The 60-day interval was chosen to try to decrease the interference of these strains with each other, and the label was crafted for that as well.

Dr. Modlin suggested saying "it is possible if not likely that children aged >5 years would respond well to one dose, but the package insert recommends two doses." Dr. Salisbury suggested that it should be noted as well that, if the child sneezes right after vaccination, the dose should not be repeated. The problem is that, this would also cause confusion because it would

differ from the ACIP recommendation on TIV. Most children are probably seropositive by age 5 and could have one dose of either, but recommending something for LAIV that was not recommended for TIV only six weeks earlier invites confusion.

The ACIP agreed to select Option 1.

"Recommendations" or "Guidelines"? This vaccine is a good technology, but this document never mentions where it should be used while devoting an entire page to where it should not be used. It was agreed to reflect the General Recommendation on influenza vaccination among these age groups and to label this as a recommendation.

It was agreed, since these vaccines are essentially equivalent in efficacy, to make positive statements about the use of this vaccine in the context of ACIP's approach to influenza vaccination. It would be recommended for the contacts of high risk individuals, as done for TIV, whether equally or with a preference for TIV for contacts of immunosuppressed persons, and permissive use for the other groups as done with inactivated vaccine, and again not stating any preference. The recommendation was drafted overnight and voted upon on the next morning.

The committee agreed to table the issue of the cost difference between the vaccines. The current tiering system for TIV calls for vaccination of healthy individuals aged 5-49 after November 1, so those wanting to be immunized before November 1 would have to pay $50 for LAIV.

Cold chain aspects. Dr. Abramson stated that the AAP will not state a vaccine preference except for the specific circumstances noted for TIV. But the LAIV storage issue needs to be addressed, as often vaccines are stored too cold and the box required for LAIV will take a lot of space away from other vaccines. He asked about the vaccine's stability in freezers not constantly at -15°C. Wyeth conducted stability studies and provide the box to hold eight 10-packs of vaccine. But the freezer still has to be monitored since the box has no temperature gauge. Wyeth has developed a lot of educational material to emphasize that the proper temperature needs to be in place and maintained before the product is shipped. But there are other devices that can be used. The document could state that technical assistance on all these products should be available to providers from the manufacturer.

Smallpox Vaccination Program (SVP) Update

CDC SVP.
Presenter: Dr. Ray Strikas, NIP.

After lunch, Dr. Modlin announced that the ACIP/NVAC Joint Workgroup on Smallpox had met to discuss possible sentinel cardiac events related to the smallpox vaccine. This will be discussed further in the next few weeks.

The *preparedness activity* of the SVP is to:
1. Provide voluntary vaccination, follow-up service and training to those individuals who would be called upon to control and contain a smallpox outbreak; develop a system to manage vaccination

adverse events; assess the legal authorities; identify and train personnel; and maintain a database of staff needed to contain an outbreak.
2. Establish/improve surveillance of rash illness and laboratory analysis to rapidly detect and investigate a smallpox outbreak; improve rash illness reporting; develop and execute an exercise smallpox response plan, and develop laboratory capacity.
3. Ensure that public health has the capacity to rapidly protect the public through large-scale vaccination; plan to store and manage vaccine; identify and train staff; develop and execute an exercise of a large-scale vaccination plan; develop communication materials.

Preparedness was planned loosely in two stages for targeted vaccinations. First, healthcare and public health teams, with the numbers of individuals and teams determined by state and local health agencies and hospitals, based on their locally established preparedness goals. Then, upon completion of Stage 1, others who may support smallpox outbreak control efforts could be vaccinated: security staff to maintain public order, EMS staff (perhaps including firefighters performing EMS duties); hospital staff and private health care providers and their staff who may be at occupational risk. Again, state and local health agencies and hospitals determine the numbers of individuals and teams.

A "natural pause" has occurred between stages 1 and 2, as continuation guidance for CDC bioterrorism cooperative agreement is implemented from May through August 2003.

Program evaluation underway includes weekly progress reporting and 11 completed vaccine clinic site visits. The participation of ER health care workers is complete; a national survey of physician attitudes, knowledge and potential participation will be done in July; that of hospital and individual participation will be done in September. Ongoing evaluation is being done of program costs, prevaccination screening and informed consent, and response to the Dryvax® vaccine. Take rates to date average 92%.

Comprehensive *vaccine safety evaluation* includes ongoing VAERS review and active surveillance at 21-28 days after vaccination, a 10- and 21-day post-vaccination phone survey, case investigations (especially cardiac), a Safety Working Group involving the ACIP, a pregnancy registry after inadvertent vaccinations, and exploration of a possible association of virus and vaccine-related adverse events due to Dryvax®' diversity of sub-strains of vaccinia. Also being followed is bifurcated needle safety, needlestick surveillance (none reported) , vaccination site care and dressings (by NIH) and communication (media coverage).

Compensation was addressed by the May 2003 law providing benefits to the public health and health care team members and to public safety personnel.

Progress to date is measured by the data reported by 55 of CDC's 62 program grantees: 37,608 persons were vaccinated as of June 13 in the civilian program and 11,700 being healthcare workers. Only about 10% of hospitals have ≥25 persons vaccinated, suggesting that regional rather than hospital response teams will be needed to manage an outbreak. In all, 289,900 doses have been released. A chart demonstrated declining SVP participation with the advent of SARS, the end of the Iraqi conflict, and the vaccine's cardiac complications. Now, only ~100 persons a week are being vaccinated, and most vaccinated individuals are in only a few states.

In addition to implementing the SVP, CDC updated the response plan for mass casualty guidelines, enhanced infection control guidelines, environmental control (decontamination), new case reporting and contact tracing forms. Work is in progress to address the issues related to smallpox vaccine pediatric use, threat assessment, and incident command.

Challenges include a low threat perception since the post-Iraq conflict, that compensation laws are not yet implemented, the cost of other lost public health work opportunities, integrating smallpox preparedness into the May overall bioterrorism guidance, and other competing public health priorities such as SARS and West Nile virus.

Next steps include continuation of evaluation and publication of findings, provision of technical assistance to states developing their cooperative agreement workplans, development of IND provision of vaccine to the general public desiring it, improving the vaccination system, and determining program reporting requirements.

Discussion: How much vaccine wastage is occurring? That is unknown and is being assessed by states. Once the vial is opened, the vaccine only lasts 90 days. There will be wastage, but some is being use for monkeypox prevention as well.

IOM Review of CDC's SVP Implementation
Presenter: Dr. Kristine Gebbie, Columbia University, IOM Committee Vice Chair

CDC requested that the IOM evaluate its pre-event SVP on eight program areas: 1) the informed consent process, 2) screening contraindications, 3) the system to assess the safety profile of the smallpox vaccine, 4) guidance for the treatment of vaccine complications, 5) professional training programs in development by CDC, 6) communications efforts, 7) CDC guidance for states in developing their implementation plans, and 8) overall progress at achieving program goals.

Three letter reports have been issued and a fourth is in preparation. The key messages of each (and the release date) are summarized below.

- (January 16, 2003) This report highlighted the uniqueness of this program and the need to proceed cautiously. *Advice:* Start Phase II only after Phase I is evaluated; use a wide range of methods for proactive communication, training, and education, and customize them to reach diverse audiences; and designate one credible, trusted scientist as the key national campaign spokesperson. *CDC response* created/implemented active surveillance for adverse events; is developing an information sheet for vaccinees' contacts; is adding information about compensation issues to the Vaccine Information Statement (VIS); and is enhancing evaluation efforts.

- (March 27, 2003) This report advised the conduct of all aspects of the SVP with the intent of advancing the goal of smallpox *preparedness*. Conduct comprehensive evaluation of the program and its outcomes to improve its implementation and to protect the vaccinees and the public. Key messages advised:

- Emphasis on the need for preparedness, not achieved through the numbers of individuals vaccinated, but through how they are deployed and CDC interactions.

Rapid program expansion may inhibit program evaluation. It may interfere with consideration of other aspects of preparedness for smallpox, bioterrorism and essential public health services and prevent development of new objectives and detailed plans. Linkages are lacking with the agencies involved in the expansion.

- Revisit the SVP's objectives in view of state-level realities, and provide a preliminary perspective on the national and state success in reaching those objectives.

- Ensure that all print materials addressed to the diverse public, now all in English and written at a grade 12 level, be easily read/understood, written in other languages, and culturally appropriate. One set of materials should be useful to all people.
- The ACIP Workgroup on Smallpox Vaccine Safety should carefully consider, when advising CDC, concurrent release of those recommendations to the public, especially if that would help transparency and maintain public trust in the program.
- In reporting adverse events, CDC should be clear what events will be reported and when, and work with DoD to decide how to report adverse events occurring in both programs. CDC should reporting regularly on the effectiveness of screening practices to identify contraindications (e.g., pregnancy, HIV status, eczema or atopic dermatitis) prior to vaccination.

- (May 27, 2003) There is now a natural pause in the process. CDC should facilitate the states wanting to pause and evaluate/plan before moving on. The pause is important to explore safety questions, perhaps to craft new case definitions, and to assess the changing circumstances. Among the latter are different vaccinees, community responders without a medical background/information base, which changes the whole process of informed consent and education programs. The IOM also called for thoughtful integration of this vaccination into a full, overall smallpox vaccination program. Comments on CDC's guidance to states included question of whether every hospital must have a response team to be considered prepared; vaccination prioritization of personnel categories, and more guidance on the vaccination time frame for the entire population. It also suggested defining "working links" or relationships as a "critical" instead of an "enhanced" capacity.

The fourth report will elaborate on these foregoing issues further and should be released soon. In summary, the IOM's key messages were that the SVP is not a typical public health campaign, but a bioterrorism preparedness campaign; taking a pause is important; and success is more than just the numbers vaccinated.

Discussion included:

- *Preparedness goes beyond smallpox as well as numbers. Will the IOM work with HRSA regarding the funding they are providing to hospitals for preparedness?* This committee has no contract from HRSA, but that broader context is what it supports.
- *How does one define "success" in preparedness? Universal vaccination of all Americans? Where does it stop?* The committee pointed that question back to CDC; no one has a clear answer. It is possible that the standing committee's next report or a following report may look at that definition. As a public health official working with NACCHO,

Dr. Gerberding felt that a lot of material on which to base that decision is lacking on a general level, let alone specifically for terrorism or its subsets.

DOD SVP Report
Presenter: Col. Dr. John Grabenstein, DoD.

Dr. Grabenstein related the thanks of the Assistant Secretary of Defense to the CDC and ACIP on its assistance in conducting their SVP program. He reported on their progress. Since the President's December 2002 announcement, DoD's Stages 1 and 2 have been completed: vaccination of response teams, health care personnel, and troops. Since early January 2003, ~500,000 troops have been vaccinated and educated about the vaccine throughout. ACIP and FDA screening standards are part of the DoD program and contraindication screening includes HIV and pregnancy. Quality assurance of the vaccinator and healthcare worker vaccination site protocols, take evaluations, documentation, and regionally pre-positioned VIG and cidofovir around the globe are done. Military-unique protocols include banned hot-bunking with vaccine-exempt personnel.

DoD SVP statistics follow:

- Vaccinations have been done in clinics of groups ranging from dozens to thousands. Rate limitations include educational time, screening for contraindications, and ensuring time for Q&A. The doses delivered per "100-dose vial" have ranged from 60 - 120 for a net of ≥64.
- Safety assessments are done on vaccination day and exemptions are logged. Only two cases of presumptive anaphylaxis were treated with epinephrine; acute events are assessed on the day 6 to 8 "take" check. DoD is now analyzing chronic, rare, delayed, and unexpected events, comparing those vaccinated and unvaccinated for smallpox.
- As of the last week, 545,000 were screened and 454,856 were vaccinated; of those, 71% were primary vaccinees (320,000) and 29% were revaccinees (134,000). The median age was 26 and the mean age was 28. Exemption rates varied by location/setting; 5-8% were personal exemptions (e.g., atopic dermatitis); 11-34% were due to household contact contraindications.
- Primary vaccination was 3 jabs and 15 jabs for revaccination, both for a 96% take.
- *Adverse effects*
    - As expected: itching, swollen lymph nodes. Only 1.3% had to restrict their activity 3% of hospital staff at Walter Reed took sick leave, and 0.5% overall did so. There were no hospitalizations.
        – 32 cases of generalized vaccinia, all mild and patients recovered. Rare inadvertent infection of skin or eye (42 self-inoculation of skin and 21 contacts and 10 self-inoculations of eye and 2 contacts with eye infection). All recovered. Two uses of VIG, one for a burn that involved the vaccination site, and one for eye contact transmission.
        – One encephalitis case, with only temporal association; CSF was negative for vaccinia and the patient recovered. The pregnancy registry lists 125 women inadvertently vaccinated (1.7 cases per 1,000 women of childbearing age) and there were 10 vaccinations of HIV-infected persons. All had takes and healed.

– No eczema vaccinatum, progressive vaccinia or death due to smallpox vaccination occurred, although a few vaccinees have died and one death was unexplained.

– One suspected myopericarditis case (EKG abnormalities) and 35 probable (per enzyme check), one confirmed; none in revaccinees. An article on the first 18 cases will soon be published; 6-8 week, 6- and 12-month follow-ups on sequelae will be done. An elevated relative risk found infers that the vaccine causes myocarditis.

– Ischemic events: 8 probable, at the 2-14 day interval post-vaccination. One MI was fatal (in a 55 year-old smoker with 3-vessel coronary occlusion and **no** myocarditis); 2 angina, 1 coronary spasm, and 1 atrial fibrillation. There was no excess of ischemic events from what was expected (~50/year in the Army and Army reserve).

Lessons learned included the following:

- Careful screening reduces adverse events to <1960s levels; VIG was needed less frequently than expected.
- Education and screening are vaccination rate-limiting steps.
- 3-15 jabs yielded high "take" rates.
- Clinicians were alarmed by the first maculopapular rashes they saw in vaccinees, but that lessened with experience.
- Secondary spread of vaccinia poses the greatest risk to bed partners.
- Myopericarditis is a greater risk than anticipated, principally among male primary vaccinees, in DoD's experience.

Dr. Grabenstein acknowledged Col. Dr. Ben Diniega, who is retiring, and who contributed greatly to the development of the DoD's SVP. Dr. Modlin also appreciated the great contribution of the DoD program, which is much broader than the federal SVP.

Discussion included:
How well can the experience of young healthy men/women in the military be extrapolated? Dr. Grabenstein thought this to be very generalizable. While there is a healthy worker effect, it is still comparable to fire, police, EMTs, etc., in terms of age. There is a differential in exercise, but the military might smoke more.

How many healthcare workers are in the denominator? All healthcare workers, hospital teams and field hospital teams total 27,000 worker months of clinical time with patients, and the social contact time of the 454,000 vaccinees is 318,000 months.

An article describing the experience of the pregnant women vaccinees will be published next week. Outcome data are expected within 2-3 weeks, but the early data indicate a normal miscarriage rate, and two products of pregnancy had no vaccinia.

What was the experience with use of VIG? There were two cases. In one, an 18 year-old male with burns on 40% of his body received IV rather than IM VIG. He developed some vesicles posterior to the vaccination site. But there was no bad outcome and these cultured negative to vaccinia, so it is unknown if the VIG played a role in suppressing vaccinia. The second case of

eyelid involvement, resulting from an intimate adult female contact, was written up in early March. When the eyelid swelling increased, the state called CDC for VIG, which was sent. The swelling reduced and she was discharged quickly. The role of VIG in her speedy recovery was again uncertain. There were also some out-patient encounters and in-patients treated for a bacterial cause.

Adverse Events Following Smallpox Vaccine *(except for cardiac events)*
Presenter: Dr. Gina Mootrey, NIP.

Dr. Mootrey outlined the status of the adverse event monitoring system, its time line, the VAERS and clinical team follow up, and active surveillance. The most recent data are posted on the CDC media relations Website every Thursday.

CDC's comprehensive SVP adverse event monitoring response system involves active surveillance, enhanced passive surveillance (VAERS), vaccination site care monitors, state adverse event coordinators, technical assistance to states, a clinician information line, a CDC clinical consultation team, pregnancy registry, a hospital smallpox vaccine monitoring system, the CISA vaccinia study, and a Cardiac Adverse Events Investigation Task Force.

Established on December 24, 2002, the states were trained on adverse event's in the following month. A time line of events since the civilian vaccination program was shared, beginning on January 24 and through to the March myocardial infarction (MI) events and CDC's responses to date.

Civilian program statistics of adverse events (AE) recorded in VAERS to date include (a list of 21 of "other" serious reports was also shared):

- 37,478 persons vaccinated.
- 694 civilian VAERS reports, 55% from revaccinees; 76% female, 61% aged 40-59; 88% non-serious according to the regulatory criteria.
- Rates: all AEs, 18.5/1,000 doses administered; serious AEs, 2.2/1,000 doses administered.
- AE Overview: 3 reports of generalized vaccinia (1 confirmed), 12 of inadvertent inoculation (non ocular, 6 confirmed), 3 of ocular vaccinia (2 confirmed) and 22 myo/pericarditis and post-vaccinial encephalomyelitis (neither of the last two groups' cases confirmed).
- One suspect PVE case, but as described in the *MMWR* article, several features of this case were not typical of PVE.
- 67 other serious reports, including 3 deaths, two due to acute MIs and one case of atherosclerosis in a 46 year-old male 10 weeks post-vaccination.

Active Surveillance is done primarily for rare, serious AEs in vaccinees. As of June 11, 2003, 10,835 valid records were submitted from 594 different facilities in 37 states/territories/major cities. Statistics to date are as follow:

- Contraindications: 26 (0.2%) identified after vaccination; medical treatment required for 219 (2%) vaccinees; 190 (1.8%) as outpatients and 25 (0.2%) hospitalized. Information was missing for four. Cardiac risk factors among 2123 records ranged from 0.8 % for CHD and stroke to 9.6% for hypercholesterolemia. Three hundred ninety-eight AEs were reported for vaccinees, 154 of them being local reactions and 214 being "other" events similar to the VAERS reports.

In summary, the civilian program has seen few of the adverse events historically associated with smallpox vaccination, and only one VIG release was required to treat a civilian who was a DoD vaccinee contact.

Discussion included note that the active surveillance listed 26 individuals with contraindications after vaccination. They were not cardiac related, but Dr. Mootrey could not answer specifically as to what they were. Determining those could be helpful. The questions on cardiac risk factors only asked about the existence of a list of contraindications, which need not be specified. There were no cardiac contraindications reported until early April when the ACIP issued guidance on that.

Cardiac Adverse Events Following Smallpox Vaccination
Presenters: Dr. Juliette Morgan, NIP SVP Adverse Event Monitoring Activity, and Dr. Grabenstein.

An overview was presented of the history of association between smallpox vaccination and myocarditis or ischemic cardiac events, myo/pericarditis case definitions, and the DoD and civilian programs' experience of myo/pericarditis and ischemic events.

Cardiac involvement is only rarely reported as associated with smallpox vaccination, and is mostly attributed to myocarditis in Europe and Australia. The vaccine used there is thought to be more reactogenic than the NYCBOH strain used in the U.S. An outline of case series and cohort studies done in Finland and in the U.S. were presented.

- Finnish Case series 1876-1981 (Karjalainene, J, et al. *Acta Medical Scand*. 1983:213:65-73).
- Finnish Cohort Study, 1974: (Helle, E-P, et al. *AnnClinical Res* 1978:10;280-7)
- U.S. studies: The 1947 New York City vaccination campaign reported one fatal case of myocarditis, but a 1963 national survey and a 4-state survey reported no cases of myo/pericarditis at all (Dolgopol, *Archives Neurol Psychiat* 1955:73;216-23; Neff, *NEJM* 1967:276;125-32; Neff, *Pediatrics* 1967:39:916-23). Neither did a national survey in 1968, but a 10-state survey in 1968 reported one 47 year-old primary vaccinee identified with transient pericarditis (Lane. *NEJM* 1969:281;1201-7, Lane, JM, et al. *JID* 1970:122;303-9).

Myo/Pericarditis Surveillance Case Definitions for suspect, probable and confirmed myocarditis were presented. Confirmation comes from histopathologic evidence of myocardial inflammation at endomyocardial biopsy or autopsy. Definitions were also presented for probable, suspect or confirmed pericarditis. The latter is confirmed by histopathologic evidence of pericardial inflammation obtained from samples at surgery or autopsy.

DOD statistics. Dr. Grabenstein presented the DoD data, indicating 3 suspect, 42 probable, and one confirmed case of myo/pericarditis. One case is pending. All of the 46 cases were in primary vaccinees, aged 18-37. Publication of the first 18 cases is pending. Finding a relative risk at a 3.6 elevation over baseline for a 30-day interval (95% CI, range of 3.3 to 4.1), DoD concluded that smallpox vaccination appears to increase the risk of myo/pericarditis. The onset interval was very tight between days 7-12.

CDC statistics. Dr. Morgan presented the civilian data of 9 suspect cases and one probable case of myocarditis, 6 suspect and 3 probable cases of pericarditis, and three cases of suspect myopericarditis, for a total of 18 and 4 suspect and probable, respectively. Details of the symptoms for each were presented. All the cardiac enzymes were in the normal range for the myocarditis presentations and for the 9 pericarditis cases. The incidence rate of suspect and probable myo/pericarditis case rates in the civilian population was 59/100,000; the probable myo/pericarditis rate was 11/100,000; and the rates of probable myocarditis and pericarditis were 3/100,000 and 8/100,000, respectively.

CDC concluded that:

- A causal association between smallpox vaccination and myo/pericarditis in DoD vaccinees appears likely.
- The evidence for a causal association between smallpox vaccination and myo/pericarditis in civilian vaccinees is unclear.
- Civilian vaccinees with myo/pericarditis were older revaccinees; DoD cases were in young, primary vaccinees.
- Potential contributing factors leading to differences in the two populations include case seeking and medical practices, primary vaccinee vs. revaccinee status, differences in physical activities after vaccination, and synergistic effects of multiple antigens received by DoD vaccinees versus the single antigen received by civilians.

Ischemic events. Ischemic events among civilian vaccinees in the literature were summarized. The French vaccination campaign to 1955 identified 8 ischemic events among 25 million vaccinees, and in Germany one person was so diagnosed in 1979. There were no recognized associations in the national or state U.S. surveys in 1963 or 1968. But there were several reports from Europe and Australia of smallpox vaccination and cardiac deaths (Lane et al, *JAMA* 1970). The data of the current SVP were presented, which supported the CDC conclusion that, while a relationship between smallpox vaccination and ischemic cardiac events is biologically plausible, currently available evidence does not support a causal association. However, the small number of civilian vaccinees limits the power to detect an association.

Data of the DoD experience were presented on eight ischemic events in recent vaccinees. They included three MIs, one fatal; two angina cases; two diagnoses of atherosclerotic vascular disease and one case of atrial fibrillation. The fatal MI case was described in the *MMWR* and showed no myocarditis. The expected 2002 active duty hospitalizations for any 14-day window were 25 ischemic admissions, age adjusted to the vaccinees, and 14 were observed. Fifty cardiovascular deaths per year are expected in the Army overall. They concluded that ischemia does not occur after vaccination at any elevated rate, compared to that of unvaccinated people.

The SVP's *next steps* include ongoing cardiac event surveillance, follow-up of identified cases using a standard protocol in development, and additional epidemiological and clinical investigations to be performed as feasible.

Discussion included:

- The DoD information has been released to the states by conference calls all along, but the March 24 *MMWR*'s focus on the cardiac events might have prompted more physicians to look for and report it.

- *Some people who have other viral causes of myocarditis, appearing to return to normal health, exhibit symptoms later in life. Will that follow-up include that consideration?* There is some concern about that possibility, but it is skewed by the presence of disease in the first place. Out of DoD's 46 such cases, 2 or 3 had substantial reductions in injection fraction and for those, a different prognosis would apply. More data are needed. However, Dr. Modlin cited an *NEJM* paper suggesting that patients with the best outcomes were those with the most severe acute disease initially among all cases of viral (admittedly, not vaccinia-related) myocarditis. There may be a disconnect between the likelihood of developing long-term chronic sequelae and severity of initial presentation.
- There is also a difference between inflammatory and infectious causes. In the evaluation of one of the myocarditis cases at the Mayo Clinic, staff were surprised that there were none with the lymphocytic infiltration expected with a viral etiology. But there was a massive eosinophilic infiltration, which suggested allergy to another vaccine component. This poses implications to long term prognosis and treatment of these individual (e.g., the treatment, paradoxically, was steroids, counter to what would be expected for vaccinia). With new smallpox vaccines to come, these events should be specifically defined as related to *this* smallpox vaccine, or a component, not all smallpox vaccines. Myocardial biopsies with ultrasound guidance would be helpful, but in the past, physicians have indicated that "these patients are not sick enough" for that.
- *An increased ischemic incidence rate in the civilian population was also reflected in the military's pattern, something highly suggestive if not statistically significant. And, was the observed versus expected angina and MI broken out by gender and age group?* Yes, the civilian program looked at males and females separately, and adjusted by gender and age group. Earlier analysis delineated deaths by gender and showed some difference, indicating that the death rate for females might be higher than expected.
- Baseline data are being collected on age/vaccine status on the 37,000+ civilian vaccinees, to enable later examination of the denominator for some of these events.

Dr. Modlin asked the committee to continue to consider the implications of the information presented, relative to the expansion of the SVP.

Preventing Inadvertent Exposure of Pregnant Women to Smallpox Vaccine; an Update from the National Smallpox Vaccination Pregnancy Registry and Public Health Investigation.
Informational presentation
Background: Presenter: Dr. Joseph Mulinare, CDC/NCBDDD.

Pregnancy is a contraindication to smallpox vaccination in the absence of exposure to smallpox. To track unintended pregnancies among smallpox vaccinees, assess the effectiveness of screening and to follow pregnancy outcomes, CDC, the DoD and the FDA collaborated on a registry of vaccination populations. It includes military personnel, civilian health-care and public health workers, and volunteers from research studies. Exposure is defined as vaccination of a pregnant woman or within four weeks prior to conception. DoD has reported 85 such exposures among 52, 185 women vaccinated; state SVPs, 8 of 7,827; and 11 among clinical research volunteers. This indicates success; since the pregnancies expected in the civilian population are 12 per 1,000, the 8 cases reported equate to 1:1000 and 1.5:1000 for the military.

Outcomes of fetal vaccinia can include fetal vaccinia, congenital malformations, prematurity, low birth weight, and spontaneous abortion. None have been reported.

Why Are Any Women Exposed?
Presenter: Dr. Karen Broder, NCBDDD.

A public health investigation was undertaken from April-June 2003 with state health departments and clinical research study investigators. Its intent was to investigate if and why pregnant women were inadvertently exposed to smallpox vaccine, and if so, whether any public health interventions might prevent future exposures. To evaluate potentially useful public health interventions, detailed phone interviews were done with civilian women so exposed, and reviews were of the cases were done by an independent external OB/Gyn physician panel. Of 19 women interviewed, ~33% probably conceived before vaccination and 66%, afterward.

Interview questions explored contraceptive practices, the use of urine HCG pregnancy tests on vaccination day, knowledge about smallpox vaccination, and the women's beliefs about pregnancy status and whether interventions might have been helpful. The screening done by the research studies and the states differed, with the former requiring a negative pregnancy test and use of abstinence/birth control to participate in the study. A full 75% of the women who conceived before vaccination day had a negative urine HCG test on vaccination day. Interestingly, although the state participants has more knowledge about smallpox vaccination and pregnancy, fewer of them were abstinent or practiced birth control before vaccination or 4 weeks afterward. The beliefs between the two groups of whether an intervention might have helped her avoid that exposure were about equal.

Since this investigation was limited by self-reports, the independent expert review was done of potential pregnancy screening interventions. Their findings were:
- Pregnancy screening is effective in the state SVP, but which components are most effective remains unknown.
- The external reviewers thought that expanded screening questions about birth control use would "likely" have been useful in preventing five exposures.
- More education about fetal vaccinia and birth control might have been useful to prevent exposures.
- It is important to evaluate interventions within the context of the population being screened.
- It is important to continue to track the number of women exposed and their pregnancy outcomes, especially if the program expands beyond healthcare workers.

Discussion included:
- The committee's response to these data varied. One member cited the "nitwit phenomenon" in which, despite having knowledge, people continued to have sex. Another was reassured at the small number of exposures after the extensive ACIP discussions of screening.
- The DoD also found 33% vaccinated pre-conception and 66% vaccinated before detectable conception, so even a universal testing policy would not have detected the latter. DoD is adding a third screening questions about pregnancy at the same time as they revise them for cardiac complications. One suspicion was that the impetus to mobilize for the war added a time imperative that did not carry over to the civilian program, that now has also reduced in the military.

- Consistency in the interviews was attempted by Dr. Broder doing them all, using a script designed by experts for clinical trial staffs' use. The 80-question survey took 30 minutes to complete.
- Emergency contraception in the event of unprotected intercourse, as was done as an adjunct to the accutane screening program, could be considered. But from a programmatic perspective, CDC wanted to begin with interventions simple to effect within the context of the SVP.
- *Is there a process to evaluate these additional screening programs to further screen out those possibly pregnant, or should ACIP comment on that?* It will be difficult to add screening questions, although they might be effective, since it cannot be ascertained what presently is producing the success of averting 7/1,000 exposures. Dr. Schwartz asked the ACIP's opinion of whether other studies were needed to determine if this or further interventions should be added. The committee's responses expressed concern that more restrictive screening risked turning away people who should not be (e.g., those with no need to practice birth control), and that additional counseling would be logistically difficult.
- *Are there not compassionate VIG releases by the manufacturers for persons discovered to be pregnant upon or shortly after vaccination?* ACIP discussed the use of VIG as a prophylactic option, the committee had little enthusiasm for the idea even though this s in the IND. The appropriate time to use VIG would be when a woman has viremia due to the vaccination (6-9 days after vaccination), and most of these women were outside that window. DoD also found no pregnancies within their 14-day window to offer VIG. Acambis reported that three women in their trials received IV VIG within three weeks of vaccination. Those data are being worked up now.
- At least one of the women surveyed thought that a serum pregnancy test would have been helpful in making her vaccination decision, but those details were not explored.

Update on Work Time Lost Due to Adverse Event or Furlough; 10 Day/21 Day Survey of Smallpox Vaccine Recipients
Information; Presenter: Dr. Arnulfo Muralles, Immunization Safety Branch

A seven-state survey of 735 interviews was completed as of May 31. Little of the 1960s data includes the range of vaccination responses or their timing. This survey reviewed the Dryvax® vaccination experience to better characterize the more common adverse events following Dryvax® vaccination, to help monitoring for any unusual or unexpected events, and to assess the resulting costs and time missed from work. Vaccinated volunteers kept diary cards and were interviewed by telephone on days 10 and 21 post-vaccination. Of these volunteers, 67% were female, 33% male; the median age was 36 years and 90% were revaccinees.

The AE's were charted, from mild to moderate and moderate to severe. Redness, itching and lesions at the vaccination site predominated at the 10 day interview, with lesser, but present, reports of muscle and joint pain. At 21 days, coughing and wheezing and neurologic symptoms (fatigue, lethargy, headache) were reported. In feedback on the prescreening education, >60% of respondents found it to be realistic; almost 30% reported that the reactions that occur with vaccination were overstated. Analysis of smallpox diary cards completed by the vaccinees at CDC indicate that persons aged <40 years old and primary vaccinees were more likely to report adverse events (e.g., chills, muscle pain, joint pain, etc.). Females were also more likely to report certain adverse events (i.e., swelling/tender lymph nodes, pain at injection site, headache).

Symptoms were flagged for follow-up after the interview, including cardiac symptoms. Of the 24 followed for cardiac symptoms, 8 were seen by a physician. One was confirmed with cardiac disease and died, and was one of the VAERS reports. The diary card in this case was not helpful in providing more information. Three were hospitalized with that diagnosis and their outcomes are pending. Overall, this 24 represented 3% of all respondents. Twelve percent of this convenience sample missed time from work, ~9% due to illness or pain; ~8% had unreimbursed costs associated with vaccination.

Discussion included comment that this was an uncontrolled study, a problem with studies of adult populations. Accepting putative symptoms makes evaluation very hard. Several suggestions of alternative studies were offered (e.g., case-control of those refusing vaccination, or following vaccinees past the point were symptoms are expected, or interviewing them for symptoms before vaccination). Some attempt to control for this was done with a comparison group who kept modified diary cards from day 30-51, when they should be back to baseline health, and were interviewed at day 41. Data analysis is not yet done.

Report of the NVAC Smallpox Vaccine Safety Workgroup
Presenter: Dr. John Neff, Workgroup Co-Chair

Dr. Neff summarized the status of the DoD and DHHS SVPs, addressed the inflammatory and ischemic cardiac events, and the options considered by the Workgroup for further work. The DoD program participants are mostly primary vaccines (70%), 87% are male, the median age is 26 years and the mean age is ~29. The civilian program has fewer vaccinees (10% of the DOD total), of which 25% are primary vaccinees and most (66%) are women; the mean/median age is 46 years. Both programs have flattened out after peaking, for different reasons.

Dr. Neff summarized the military experience related by Dr. Grabenstein. The civilian program had 76 cases reported to VAERS; 8 pregnant women were inadvertently vaccinated; and there was one case of post vaccination encephalitis. This demonstrates the success of screening.

The number of inflammatory cardiac events was insufficient to determine significance in the civilian population, but the military program suggested that vaccination seems to increase myo/pericarditis. The ischemic events did not exceed the expected level in the population.

- Evaluation of cardiac events indicated that they were biologically feasible. A causal relationship between smallpox vaccination and ischemic cardiac events appears unlikely, but the data are insufficient to know with certainty. In the absence of certainty, the current deferral recommendations for the pre-event program should remain.
- Additional investigations of ischemic events should be undertaken: surveillance, investigation of new cases and periodic review of observed versus expected rates of events. DoD data should be reviewed.
- Causal relationship between vaccination and inflammatory heart disease is indicated by DoD data, that reflect a significantly higher risk of myocarditis than the background rate..
- Post-vaccination guidance to vaccinees should be provided about suspected association with inflammatory cardiac disease, uncertainty about potential association with ischemic disease, and any known risk factors for these conditions. Educational materials on symptoms should be provided that could prompt examination for myo/pericarditis, etc.

- Current education and informed consent material should be expanded beyond the current narrow focus and translated to the appropriate literacy level.
- Studies to investigate biological mechanisms for cardiac adverse events are indicated. Future trials should collect prospective clinical and pathophysiological information relative to ischemic and inflammatory events. Baseline and follow-up of ECGs and optimal virological studies are needed to explore alternative etiologies. So are prospective studies of cytokines and other markers for inflammation post-vaccination, as well as other possible associated factors.
- Additional inquiries that should be done include developing criteria for standard review and follow-up of identified post-vaccination myocarditis, ascertaining long-term health consequences, doing retrospective case-control studies, creating a central case registry, and a large cohort follow-up study of long term morbidity and mortality. The latter is very important since signs, particularly of cardiomyopathy, may emerge later. Animal studies should be done to follow up.

SVP Evaluation to Date.
The Workgroup's evaluation of monitoring activity explored whether the mechanisms to monitor smallpox vaccine adverse events have provided sufficient and timely data to assess safety, and whether available data give a reasonable indication of adequacy of screening procedures and materials. The answers were both a resounding yes. CDC was congratulated on excellent follow-up work on all cases, almost immediately after they occurred.

The Workgroup assumed, and agreed to, the continued preparedness to stockpile smallpox vaccine at strategic regional and local facilities, continued planning and education on vaccination practice and the optimal response to an introduction of smallpox, and continued evaluation of the ongoing levels of risk of smallpox introduction and the level of risk from the vaccine. The latter was felt to be extremely important.

SVP Options.
Options for the SVP considered were: 1) to stop vaccination even on a voluntary basis; 2) stop the vaccination program but allow voluntary vaccination for potential first responders; 3) continue the current pre-event voluntary program, vaccinate selected public health and first response health care workers with careful screening of known risk factors, to meet and maintain state/local health department readiness needs; or 4) begin Phase Two.

The first two options were the minority preferences, due to the major and unexpected event of myocarditis, the unknown frequency of mild forms and the sequelae of these conditions; and the unknown risk factors to be incorporated into screening. However, the majority preference was for Option #3. This would maintain the pre-event volunteer vaccination program at a slow rate, eliminate the goal of 500,000 vaccinations for the country and provide health departments with the latitude to determine their own state of readiness. No Workgroup member favored Option #4.

Discussion included:
- *Is there any way to determine the reality of how many people will continue to present themselves as responders for vaccination given the publicity about myocarditis?* There is no easy answer. Evaluations underway of why people did or did not participate may

inform this, as will the states' work plans (to be received by July 1) to determine the organizational level of their plans.

Dr. Birkhead reported ASTHO's related national conference call on June 4, during which 18 different states reported varying program status. Most were continuing Phase 1 at a low level; some were moving ahead with broader vaccination, but most have not found a big responses. New York stopped programs for two weeks due to the cardiac events and found much less interest when they restarted. They will focus on defining preparedness in terms of whole variety of factors: training, checking negative pressure rooms, conducting drills, etc. More vaccination may be offered as hospitals determine what more they need to do. Police and fireman, even the FBI staff stationed in NY, have shown minimal interest.

In Texas, Dr. Hanson reported much variability in the program but a gradual tapering off across the state. Workplans will focus more on defining work with partners and who should be defined as response staff. Dr. Finger reported the Colorado's health department's opinion that they are ready, particularly since they have a big military (and therefore vaccinated) presence in the state.

- *Still, the problem remains of making any recommendation without some assessment of risk. Was that discussed?* The workgroup's charge was to consider the safety of the vaccination program. Considering the optimal safety for the population, the minority felt that the program should be stopped, but evaluating this in terms of risk was not their charge, but the ACIP's.

When will the Acambis cell culture-based vaccines available, and being from the same strain, will they have any different safety profile than a vaccine grown in calf media? No one could speculate on the likely licensure, although the trials are progressing on schedule. Dr. Birkhead expressed New York's assumption that the present vaccine will be used for the next year or so.

Pediatric vaccine use. Dr. Katz asked if, based past experience, the reassurance of almost no serious adverse events and little transmission, the data would differ if children were included? Since past surveillance was so much less precise than now, Dr. Neff could not say what degree of myocarditis or encephalitis may have existed in the 1960s.
Several comments were offered in favor of stopping the program:

- Dr. Lane agreed. The extensive present screening was not done and the technological tools of cardiac enzymes or echocardiagrams were not yet available. He agreed with Dr. Gebbie's emphasis that this program is *part of* a general terrorism response. A tremendous amount of work has been done to totally rebuild and modernize a vaccine supply and the VIG supply; to train and raise consciousness about smallpox and to plan at multiple levels; all despite the absence of any new information of an increased risk. He agreed with the Workgroup members who felt the time was right to stop the program.
- Dr. Abramson suggested that the ACIP return to its initial recommendation that only 10,000-20,000 people be vaccinated nationally (~200 per state). That level of readiness is well on the way to being accomplished.
- Dr. Neal Halsey advised the ACIP to learn what the states are planning in case of an event, because it could assist that decision. FDA has no data to support the use of the vaccine, but he suspected that if smallpox were used as a bioterror agent, most of the ACIP would support

its immediate use. FDA should be asked what it would need to declare that. However, he also did not think that pediatric studies were yet needed.

- Dr. Paul Offit supported the option of ceasing vaccination, and asked specifically for ACIP to consider what its "stop" position should be. He felt it should be upon low risk, and this seemed to be the time.
- Dr. Pierce Gardner, who participated by telephone, commented on the ethical difficulty of saying not to immunize people potentially not be at risk but who would still deliver the vaccination. He felt that, once the answers to the long-term consequences and incidences of subclinical myocarditis are known, as well as what the real threat level is, the ACIP would be in a better position to proceed. But, he felt, that was not now the case. He expected to have more information in the next 6-12 months from the military's prospective examination of vaccinees for myocarditis. He urged that safety be put ahead of the program to support the public's vaccine confidence in general. Dr. Bob Chen of the NIP reported that DoD would work with NIP and the CISA network on a close clinical follow-up of vaccinees in the next 6-12 months.
- Dr. Siegel reported the HICPAC Safety Committee's reluctance to endorse proceeding to Phase 2 for several reasons, including because that will involve infection control issues and potentially less careful site care.

FDA Considerations

Dr. Baylor stated that FDA would need data to support a new vaccine's use among a pediatric population; without that, they could not recommend that indication. But whether it would be recommended for use in a pediatric population off label is not up to the FDA. Dr. Modlin commented that a vaccine is already licensed for administration down to one year of age, but it would have to be used under an IND.

Dr. Orenstein announced NIP's work with the FDA to develop a streamlined process in the event of an attack that would not require a 45-minute screening test, and confirmed that the IND would include all ages. The NIH pediatric trial was to ensure that the 1:10 dilution that was to be licensed would be sufficiently robust if used in a pediatric population. But with the licensing decision changed, the only question left is for Acambis or any new product to address how to deal with children.

Suggestions relative to Option 3 were:

- A modification of Option 3 to indicate that it is too early to implement Phase 2 and that a pause, as recommended by the IOM, is indicated.
- The latter part of Option 3 permits state health departments to determine their readiness/preparedness, but guidance on what that means needs to be developed by the ACIP so that at least some basic aspects are met. However, Dr. Stratton reminded the ACIP that the IOM committee is restricted in what recommendations it can make; it was only charged to examine how most safely to implement the SVP, and the pause was discussed from that perspective.
- Dr. Orenstein agreed to the discomfort of making a national security decision without new information. However, while the cardiac events were unexpected, he noted the far fewer occurrence of those that were expected. He also was concerned about potentially discouraging the states still trying to get their response teams in place or making replacements with staff changes.

- Dr. Modlin agreed that there would be better follow-up data from the cases that have occurred so far. But, with falling vaccination rates, incidence data is likely to be in the low numbers. While those data would be helpful, they will be insufficient to be substantially help the ACIP's decision. The DoD/CISA data will provide more information about natural history, but not about rates.
- Dr. Neff stressed the Workgroup's strong opinion that the nation should continue to stockpile smallpox vaccine and continue preparedness.

Dr. Levin summarized a general feeling among the committee that, since some problems have not appeared while other new ones have, it is wise to proceed slowly. He was comfortable with staying on the present course, Option 3. Others agreed, but also expressed concern that states not be advised to proceed to Phase 2. Some states may have the perception that, since they did not vaccinate the initial target numbers, they have to continue. Dr. Plotkin advised ACIP to provide direction and interpretation of the safety data presented, but not to advise continuation on to Phase 2 until ACIP states its endorsement of that.

Dr. Joe Henderson, CDC's Associate Director for Bioterrorism Preparedness suggested that the committee delay its decision until the states' plans could be provided to the workgroup. The CDC grants will provide them with $100 million, and he knew of four states already planning to begin Phase 2 with those resources. He expected more development of mass vaccination planning, but not a lot of movement to offer vaccine to wider audience. Since the SVP has been tied to overall preparedness activities, the states have benefited, despite no additional information of a change in the threat level. In addition, the CDC director is already reviewing multiple recommendations on this (e.g., from the GAO, IOM and NVAC).

However, the downside of staying the course was noted: the safety issue that affects the present level of ~100 vaccinations per week. The lack of risk factors useful to screen out those at risk challenges public trust and the voluntary nature of this program, and a definition of preparedness is needed from CDC, not the ACIP.

Dr. Birkhead suggested as a compromise, since some states have already begun Phase 2, that ACIP resist advising against that. Rather, it could *express concern about vaccine safety and any vaccination taking place beyond what has been recommended, and that states should only continue if they feel it is critical to their preparedness.* Dr. Zimmerman **moved to adopt** that suggestion as a recommendation. There was to some voiced support for a permissive statement that allows states to be prepared at whatever level they think is appropriate.

Dr. Modlin asked Dr. Birkhead and the program staff to draft recommended language for the committee's vote on the following morning. He also planned to discuss subcommittee membership with the members to finalize this by the meeting's end. With no further comment, the meeting adjourned at 5:55 p.m. and reconvened at 8:00 a.m. the following morning.

JUNE 19, 2003

Recommendation on the SVP
Dr. Birkhead read the draft ACIP statement developed by the ad hoc workgroup on the previous evening.

It stated that it is critical for smallpox preparedness planning to go forward in the context of broader terrorism and emergency response planning at the federal, state and local levels. It cited the related activities, to which more could be added, including surveillance of early cases; procedures to investigate possible cases and to institute immediate control measures, to develop plans at the hospital, community and regional level; to care for smallpox patients in the event of an outbreak; and plans for mass vaccination of large groups, up to the entire population, in a short period of time.

Planning activities would include training of public health and health care personnel as well as staff of mass vaccination clinics; development of educational materials to be directed at many groups, including the general public; development of lab capacity; formation of vaccine stockpiles and necessary supplies and equipment; and the conduct of drills and exercises. And, in the context of such plans and activities, smallpox vaccination to establish and maintain healthcare and public health response teams necessary for state and local preparedness.

Specifically, the statement advised that: "At this time, the ACIP feels it is unwise to expand beyond its current pre-event smallpox vaccination recommendations because of the new and unanticipated safety concerns (i.e., myo/pericarditis), whose extent and severity, particularly of long-term sequelae, are not yet known.

A final paragraph was inserted at the request of the state representatives:

> "Any vaccination that does occur should be carried out only within the context of the currently recommended response teams and state and local response plans, and should be administered according to currently recommended vaccination procedures and protocols."

Dr. Tompkins **moved to adopt the draft statement** and was seconded by Dr. Zimmerman.

Discussion included:

- The AAP's concern was expressed about cross-inoculation, since Phase 2 would involve many volunteer fireman who do other things such as, potentially, working in daycare centers. Conducting the program "according to vaccination procedures" should be stressed, as should onsite management of dressings/wounds, etc. Reference is needed to the supplemental guidance issued on the latter.
- Dr. Schaffner stated that the National Society of Infectious Diseases would support this statement.
- Dr. Salisbury suggested, rather than saying "because" of the safety concerns, only referencing them, since the present text suggests that upon resolution of the cardiac problems, the program would be extended.
- Dr. Halsey suggested clarification of the word "its" to be "the current ACIP recommendations," to clarify that the committee does not now intend to reach the 500,000 population.
- Dr. Jackson suggested that the final text emphasize "extensive public awareness and education."

Vote: No members were conflicted with Wyeth.
In favor: Birkhead, Brooks, DeSeda, Gilsdorf, Finger, Levin, Poland, Tompkins, Zimmerman, Hanson, Modlin
Opposed: None

Abstained: None

The motion unanimously passed.

Completion of the Revision of ACIP recommendations on LAIV
Presenter: Dr. Scott Harper, NCID.

The changes made to the supplementary statement on LAIV, based on the previous day's discussions, were:

- "Guidelines" were replaced with "recommendations" and "concurrent" with "simultaneous" in the title.
- The swine/poultry worker contraindication was removed
- More language was inserted to emphasize who may receive LAIV (pp 2,3,9) to discuss the positive aspects of the vaccine.
- A section was added to insert the current recommendations for influenza vaccination (in general) from the annual ACIP recommendations (Pg 8)
- The revised recommendations for LAIV's use were inserted, followed by a list of persons who should receive TIV rather than LAIV (Pg 9):

  "LAIV is available as an option for vaccination of healthy persons aged 5-49 years, including persons in close contact with high risk groups and those wishing to avoid influenza (see Tables 1 and 2). Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response, its ease of administration, and the acceptability of an intranasal rather than intramuscular route of administration. (1)"
- The subsection on influenza antiviral use was moved up in the document to put more emphasis on that concept. (Pg 10)

- The close contacts of those at risk for complications from influenza were cited. (Pg 10)

  "Close contacts of persons at high risk for complications from influenza should receive influenza vaccine to reduce transmission of wild type influenza viruses to contacts.

  "There are no data assessing the risk of transmission of LAIV from vaccine recipients to immunosuppressed contacts. In the absence of such data, use of TIV is preferred for vaccinating household members, healthcare workers and others who have close contact with immunosuppressed individuals, because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the immunosuppressed individual and cause disease.

  " For vaccination of healthy persons aged 5-49 years in close contact with all other immunocompetent high risk groups, there is no preference between TIV and LAIV."

- More information was added on the dose divider clip, as were recommendations on what to do if the vaccine recipient sneezes (Pg 11)

- Text on dose 2 in children stated that children aged 5-8 years previously vaccinated at any time with TIV or LAIV require only a single dose of LAIV and do not require a second dose. (Pg 12)

- Pg 12 and Table 1, simultaneous administration of other vaccines, state:
  "It is unknown whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine. In the absence of specific data indicating interference, it is prudent to follow the ACIP General Recommendations on Immunization (REF). Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. An inactivated vaccine can be administered either simultaneously or at any time before or after LAIV. A live vaccine not administered on the same day should be administered ≥4 weeks apart when possible."

- "Administration of LAIV should be deferred until after the acute phase of a febrile or respiratory illnesses" was added. (Pg 12)

- Additional sources of information were added to the section on storage of LAIV. (Pg 14)

- Table 1: The order was changed and entries were edited on the simultaneous administration; non-simultaneous administration of live and inactivated vaccines was added. (Pg 16)

Discussion included the following suggestions:

- In the text on high risk contacts, delete the term "immunocompetent" and keep the term "high risk". (Pg 10)
- Grammatical edit: <u>two</u> live vaccines ... should be administered..." (Pg 12)
- Cite the advantage of cost for the TIV vaccine in the table.
- Define the term "healthy" with, for example, "(i.e., not a high risk of complications of influenza)"; and the febrile illness statement on page 12 conflicts with the General Recommendations and statements for all other vaccines. Define what the "acute" phase means, even internally, so CDC can provide guidance when asked. Advise how to deal with off-label use, which will occur? Will it be given to children <5 and people >50; should they count the dose or not, and should they repeat the vaccination because it is not indicated for the group?
  Response: Dr. Zimmerman advised that all vaccines given to people <5 and >49 are likely to be effective. Count them as valid doses; for unhealthy people, just advise that the published data are not adequate for licensure.
- Dr. Abramson suggested that a Q&A be developed and placed on the Website to answer the many questions not possible to answer at this meeting. The Influenza Branch will discuss this with the NIP.
- To the table, add a row to address the context of high risk (e.g., to balance the statement to not administer LAIV to children at risk of complications with influenza, but to do so for healthy people with close contact to them).
- Change the title to reflect the age limitation.
- Reference to the manufacturer's freezer box, have the text just ensure that the temperature is maintained, either by freezer box or other mechanism. (Pg 14)
- For readability, spell out TIV a few more times in the document until the field gets used to the acronym).
- Make the antiviral use more consistent with the label. State that the basis of the recommendation on the concurrent use with antivirals is because of the as-yet unevaluated potential of interference with a live virus in the antiviral.

Dr. Zimmerman **moved to accept the LAIV statement as amended** and was seconded by Dr. Tompkins,

Vote: No conflicts with Aventis Pasteur, MedImmune, or Wyeth.
In favor: Birkhead, Brooks, DeSeda, Gilsdorf, Finger, Hanson, Levin, Poland, Tompkins, Zimmerman, and Modlin.
Opposed: None
Abstained: None

The motion passed unanimously

Vaccine Supply and Administration Tiering
Dr. Paradiso raised the Healthy People 2010 goal to vaccinate 120 million people by 2010. Since FluMist® is likely to be available in August and September, he suggested expanding the timing of vaccination to utilize earlier vaccination opportunities. Dr. Modlin recalled the suggestion from the National Vaccination Summit to modify the ACIP's tiering recommendation. This could be done as a supplementary statement for next year's season or as a simple support for this concept. Dr. Orenstein stated that NIP could know by August if the tiering is necessary, so a revision of the tiering system would not be too late for this year. NIP would make that decision in consultation with manufacturers and FDA on availability.
Other considerations discussed included the need to be consistent with other committees' statements on the vaccine supply. Dr. Fukuda relayed the Influenza Branch's understanding that the field's familiarity with the tiered approach supported the ACIP's retention of it this year, despite no indication of a vaccine shortage. Dr. Tan was the AMA's Co-chair with CDC on the Summit. He explained that their intent was not to change or abandon the two-tier approach, but to provide a provision that the NIP, in times of plenty, could encourage vaccination of healthy adults from October through December.

Dr. Orenstein stated that only anecdotal data is available on the impact of the tiers on adult immunization in the last year. Dr. Matt Williams, of the Community Immunization Providers Group, reported their support at the Summit to expand the vaccination period from 4 to 8 weeks to allow more time to schedule immunization at nontraditional sites and at earlier clinics, which now are mostly in November. Most retailers will not sponsor the clinics after Thanksgiving.

Dr. Zimmerman **moved that ACIP ask the NIP to assess the influenza vaccine supply each summer and to relax the two-tiered approach if the supply is good.** The motion was seconded.

Vote:
In favor: Birkhead, Brooks, DeSeda, Gilsdorf, Finger, Hanson, Levin, Poland, Tompkins, Zimmerman, and Modlin.
Opposed: None
Abstained: None

The motion passed unanimously

Vaccination to Prevent Bacterial Meningococcus in Cochlear Implant Recipients
Presenter: Dr. Karen Broder, NIP

At question: Is meningitis among cochlear implant recipients potentially vaccine-preventable? If so, should ACIP change its pneumococcal vaccination recommendations for persons with cochlear implants according to a high risk schedule, since they may be at high risk for *S. pneumoniae*?

Background: Cochlear implants allow the perception of sound for those who are deaf, and are approved for children aged >12 months. Last summer, FDA issued a warning after receiving reports of bacterial meningitis among cochlear implant recipients. A manufacturer voluntary recalled one model of cochlear implant device. CDC, FDA and state health departments conducted cohort and nested case control investigations of children aged <6 years at the time of their implant between January 1997 to August 6, 2002. The final results are under review.

Incidence. As of October 2002, there were 91 cases of post-implant meningitis, and 17 deaths. The U.S. accounted for 52 cases over a 14 year period among people aged 18 months – 84 years; most were aged <7 years. Meningitis onset occurred < 24 hours to >6 years post-implant and the most common pathogen was *S. pneumoniae*. In October, 2002, CDC issued recommendations for high-risk pneumococcal vaccinations in response. They are still in effect.

It is possible that pathogens can travel through the ear canal along the implant and through the middle ear to directly contaminate the CSF space close by, increasing the risk of meningitis. By September 2002 in the U.S., 15 cases of *Streptococcus pneumoniae* meningitis occurred among 29 cases of post-implant meningitis. Twenty-one of those cases were sporadic meningitis (post-implant, as opposed to perioperative meningitis) and 11 of those were *S. pneumoniae.* Of the other 10 cases, five were *Haemophilus influenza*. Two were *Acinetobacter baumanii,* two others were E*nterococcus* species and*E. coli*, and five were unknown).

A comparison of bacterial distribution of post-implant meningitis with the distribution of both bacterial meningitis and bacterial otitis media in U.S. children showed Neisseria meningitis as accounting for much of the former, which was not reported in the post-implant cases of known etiology. S. pneumoniae accounted for >75% of the otitis media. These data support the otogenic mechanism for meningitis. High-risk pneumococcal vaccination schedules vary by age. The age distribution of children with post-implant pneumococcal meningitis was charted. It was concentrated among children aged 24 to 48 months, and all were <60 months. Most would have been eligible for vaccination with both pneumococcal vaccines before their onset.

Summary:

- *S. pneumoniae* is the most common pathogen in both pediatric and adult cochlear implant recipients with bacterial meningitis of known etiology
- The rate of pneumococcal meningitis in young children with cochlear implants is ~30 times higher than the rate in the general pediatric population
- The rate of pneumococcal meningitis is highest in the first month following the surgery but increased risk persists beyond the perioperative period.

Vaccine preventability. Data suggest that some cases of pneumococcal meningococcus are potentially vaccine-preventable. None of the 15 children studied were vaccinated with the as-yet unrecommended PPV23 and 12 were not vaccinated with PCV-7. Of the 12, only one serotype was known (35B), and only one was known (10A) of the remaining three vaccinated with PCV-7. This study was conducted before PCV-7 was generally available, but current vaccines could have prevented many of these cases.

Available information does not suggest that an expanded use of Hib vaccination or use of meningococcal vaccination would likely prevent post-implant meningococcus. Future monitoring is indicated.

- Post-implant meningitis occurred in 2 of the 24 meningitis cases of known etiology (*NEJM*, Vol.349:435-445; July 31, 2003, No.5, and FDA passive surveillance data).
- Non-typeable *H. influenzae* occurred in 3 children, but lab serotype confirmation is unknown.
- The rate of Hib meningitis appears to be higher in young children with cochlear implants than in young children in the general population.
- The rate of Hib meningitis among older children and adults with cochlear implants is not known, but only one U.S. case of post-implant H. influenza meningitis has been reported in persons aged ≥5 years. The type and vaccination status are unknown in that case.
- Two pediatric cases were immunized (although one without a booster dose), but both had significant contributing past medical histories. No cases of meningococcal meningitis have been reported among cochlear implant recipients of any age.

Summary: There is an increased risk of bacterial meningitis among cochlear implant recipients. Children with cochlear implants are at ~30 times increased risk for pneumococcal meningitis. Data suggest that some cases of pneumococcal meningitis are potentially vaccine-preventable. Available information does not suggest that expanded use of Hib vaccination or use of meningococcal vaccination would likely prevent post-implant meningitis; future monitoring indicated.

Question: Should ACIP change pneumococcal vaccination recommendations for persons with cochlear implants? The reasons to change the pneumococcal vaccination recommendations for persons with cochlear implants include: 1) an increased risk for pneumococcal meningitis among children with cochlear implants (~30 times increased risk) and that S. pneumoniae is the most likely etiology for pediatric and adult post-implant meningitis cases. An applicable ACIP high-risk indication would be the presence of CSF leaks.

Three recommendations were suggested to the ACIP:

1. "Children aged 24-59 months should receive PCV7 vaccination if they have or are scheduled to receive a cochlear implant. The high risk schedule should be followed."
1. "Persons aged 2-64 years should receive PPV23 if they have or are scheduled to receive a cochlear implant. Cochlear implant candidates and recipients should receive PPV23 vaccination according to the schedule used for persons with chronic illnesses. Cochlear implant candidates and recipients aged ≥2 years who have completed the PCV7 vaccination series should receive one dose of PPV23 ≥ months after vaccination with PCV7.
2. "Persons planning to receive a cochlear implant should be up-to-date on age-appropriate high risk pneumococcal vaccinations 2 or more weeks before surgery, if possible."

Discussion included:

- *Are there data on the referenced adolescents and adults?* The study provided good information on the children aged <6 years; the data for those older are from FDA. Of the 52 reported cases of post-cochlear implant pneumococcal meningitis, the study identified 29, but they may overlap in the 52 cases reported.
- The point is that they may not be the only children at risk; perhaps the recommendation should be more comprehensive.
- *The pneumococcal vaccine induces bactericidal antibodies in the circulation, but how would it work? It would require a transudation of antibodies into endolymph or the auditory canal. Is there evidence from similar situations to indicate this?* A literature review produced no study specifically addressing the efficacy of pneumococcal vaccination among persons with CSF leaks. The serotype distribution is likely similar to that in the inner ear, but due to the direct extension mechanism, the vaccine may work differently than it does in a hematogenous spread. An expanded recommendation might help to answer that question.
- Post-marketing information on children with CSF leaks from any cause may be available from the Phase 4 Northern California Kaiser studies. But there are data that ear infections can be prevented with serotype-specific antibody. It is not as highly effective as against invasive disease, but there may be some effect from eliminating bacteria in the middle ear or having some immune response in the ear. There will never be controlled data on this; such a trial would be unethical. The only information will come case-control and retrospective studies.
- The 2003 Redbook designated those with cochlear implants as a high risk group and advised the use, depending on the age, of both conjugated and unconjugated vaccines. The U.K. has also recommended that children with cochlear implants be vaccinated with a choice of vaccine based on age.
- *Are there any data on the different risks of the different types of implants?* The recalled implants included a component called a positioner, which may cause meningococcal meningitis, but there have also been reports on those without the positioner. The data indicate that ALL cochlear implants pose an increased risk of pneumococcus.

Dr. Zimmerman **moved to accept the recommendations 1, 2, and 3 as written.** Dr. Brooks seconded the motion.

Discussion included:

- *What is the age distribution of these procedures? Could adolescents and adults be at similar risk?* Information comes mostly from pediatric study, but due to the otogenic mechanism, these recommendations could be extended to all persons. The program suggested the use of established ACIP age-appropriate schedules; Option 3 would include all persons.
- *The implants are approved for those aged >12 months, but the recommendation only begins at 24 months.* It would be worthwhile to reinforce that children should be on schedule for their routine pneumococcal vaccinations.
- *Should we not also recommend Hib vaccine for both children and adults? Is there any indication that implant-associated meningitis is H. influenza type B?* The only data is from the FDA; only one adolescent post-implant case recorded was of an unknown type.

- Dr. Modlin suggested adding the ACIP imprimatur to the current CDC recommendations and addressing these other issues in more detail when the statements are revised. Specifically, CDC was encouraged to examine the H. influenza issues in more depth. Perhaps subsequent guidance could address the question of whether H. influenza, pneumococcal, and even meningococcal carriage rates (potentially as high as 10%) could be prevented.
- However, most adults carry non-typeable pneumococcus, as do children, which the HiB vaccine would not prevent.
- *So, should adults get only the polysaccharide vaccine and not the conjugate? The polysaccharide will not reduce the colonization of potentially virulent strains. It may be wiser to recommend the conjugate for adults, followed by the polysaccharide.* That is an ACIP decision; the current PCV recommendation goes only to age 59 months.
- Dr. Modlin defined this as a bigger issue than could be addressed at this meeting, but it should be raised at the statement revision or even beforehand. Dr. DeSeda raised another question requiring address, for long-term implants, of whether a booster vaccination would be needed.
- Dr. Katz suggested that CDC issue a memo to clinical microbiology labs to serotype isolates from patients with cochlear implants, and if they cannot do that, to send them to CDC to determine if there are serotypic correlation with the vaccine strains.

Dr. Modlin summarized, to no disagreement, the committee's **consensus to approve the three recommendations.** Dr. Wharton summarized that, as the pneumococcal vaccine statement is revised, these recommendations will be incorporated. In the meantime, they will be part of the ongoing CDC recommendations for management of these patients. As new information enables a better risk estimate, that will be presented to the committee for fuller discussion.

Use of Smallpox Vaccine for Prevention of Monkeypox
A small number of ACIP members participated in a recent urgent teleconference on the monkeypox outbreak and in the recommendations recently issued by NIP/CDC.

Overview
Presenter: Dr. Jane Seward

Since CDC's interim guidance on the use of smallpox vaccine for the prevention of monkeypox was issued, some questions have arisen and revisions are probably needed.

The first human case of monkeypox in the U.S. reported to CDC was on June 4; a retrospective case finding determined the first case to have occurred on May 1. *MMWR* published the multistate outbreak which by 2 p.m. on this day was in six states. Monkeypox is a rare zoonotic disease of African rain forest areas. It has a similar but milder presentation to smallpox, with lower case fatality and secondary transmission rates (~10%) and case fatality rates between 1%-10%. There have been no known human fatalities outside of Africa.

CDC guidance (infection control, exposure management, case definition, embargo order to certain rodents and prairie dogs, lab specimen collection) has been issued under an NCID lead. Multiple response teams are interacting with other government agencies and affected states.

Smallpox vaccine can be given under the Phase 1 SVP or under the two standing INDs for vaccination of laboratory workers or for monkeypox. Four to six states have used smallpox

vaccine for this outbreak, but different issues are involved than those of animal exposures. The animal component of this is complex; their ability to transmit is uncertain, for example.

Multistate Outbreak of Monkeypox, June 2003
Presenter: Dr. Joanne Cono, Bioterrorism Preparedness/Response Program

The monkeypox outbreak in the U.S. began with a family who adopted a prairie dog with a skin rash. It bit a child who developed pustules in May, from which monkey pox was isolated, and the prairie dog subsequently died. The Marshfield Clinic identified an orthopox virus in the skin lesion, later identified as monkeypox. It was traced back to a Gambian giant pouched rat, imported from Africa, which mixed with other caged animals in Texas and Iowa. People in Indiana, Illinois, and Ohio interchanged these animals at animal swap meets, which have few records of the transactions. But other animals in that African shipment (mice, squirrels, etc.) were listed, which CDC is trying to locate.

Eighty-seven cases of monkeypox are now under investigation in Wisconsin, Indiana, Illinois, Ohio, Kansas and Missouri. There have been no deaths. Specimens from 82 patients are under CDC lab investigation. Every case has been in contact with infected animals; there has been no known airborne or human-to-human transmission. There have been 20 lab-confirmed cases of monkeypox, 60% among males of a median age of 29 years old. Twelve were hospitalized for isolation due either to local uncertainty of how to address the disease or because the patients could not isolate themselves. Two of the 13 had previously received smallpox vaccination. Clinical presentations were described (rash, fever, respiratory and lymphadenopathy).

There was one severe outcome. A 6-year-old girl exposed to a prairie dog on May 19 had developed pharyngitis and a pruritic vesicular rash on her face, trunk, extremities, palms and soles by May 31. By June 4, she was in respiratory distress and was diagnosed with encephalopathy and perhaps seizures (described as tremors). Multiple lab tests were negative until a PCR skin biopsy was positive for monkeypox.

An interim national monkeypox case definition was released by CDC on June 17, comprised of clinical, epidemiological and laboratory criteria. Monkeypox case classifications for suspect, probable and confirmed cases were presented at this meeting, as were websites for information and daily case counts. Outbreak control measures instituted were:

- Standard contact airborne precautions.
- Fever surveillance of the exposed person (21 days for temperature ≥101.5F measured twice daily).
- Smallpox vaccination.
- Blood safety issues under discussion with the FDA for both case donation or receipt of blood in the last 28 days.
- A CDC animal importation embargo on rodents from Africa, and a CDC/FDA embargo on interstate transportation and collection of these animals.
- Educational and communication products were developed.

Discussion included:

- The importation from Africa was not expanded to include all countries, so that CDC could begin from the direct link and indigenous animals. An international team is tracing back to see if there also have been outbreaks in other countries.
- *Is the absence of human-to-human transmission part of its natural course, or only in this outbreak?* This is just for the U.S. outbreak. In Zaire, there seemed to have been cases of human spread and Congo data are clear about secondary person-person transmission (~10%) to unvaccinated household contacts, and lower than that to unvaccinated casual contacts. Some of the intervals in the U.S. cases look suspicious, but since they are all among persons with a sick pet in the household, that cannot be separated out. Much more data are coming in; this is all very preliminary.
- *Have healthcare workers been infected?* One state has reported such exposures and they are being carefully studied, including with serological testing, although the latter is a research tool at this time.
- The guidance included not to release these animals into the wild and to notify animal shelters or clinics, with advice to vets and an shelters to take infection control measures.
- *Were any of these cases reported through the smallpox rash illness hotline or the Emergency Operations Center (EOC), or was it apparent that this was not smallpox?* Most states decided it was not smallpox, but Wisconsin did call the EOC and was directed to the rash illness hotline.
- *How did animal-animal transmission occur; could there be an endogenous focus?* Currently, information is preliminary. The animals were kept in close quarters; CDC is working with USDA in those investigations. But there is a least one animal-to-animal transmission from a domestic prairie dog pet to a new sick one. There were also human cases associated with both animals. It is believed that other animals can be infected; in nature, the host range is relatively broad, especially among rodents. Chronicity of infection and transmission is not known, but animals are recovering well from the illness.
- *With such implications to animals and humans, why is there not a buy back program in addition to tracking them down, to destroy those animals (as in the case of mad cow disease), rather than passive surveillance?* Animals are being euthanized as they are found, but there has been a leveling off in the cases. And. pet owners very attached to their animals do not want to put them down if they are well. Most of this is the USDA's domain, and studies of surrounding animals are being done due to great concern about transmission to domestic animals.

New Jersey Health Department Experience
Presenter: Dr. Eddie Bresnitz, New Jersey State Epidemiologist.

A suspected case of monkeypox occurred in New Jersey in an 11-year old boy who had moved there from Indiana. Before moving, he had an illness with a high fever and a cough, was treated with antibiotics, and returned to school. He had played with a few prairie dogs before moving and, since a chronic carrying state of monkeypox is unknown, he was treated as a suspect case.

When he then developed a vesicular rash, in different stages of eruption, and he saw monkeypox on TV, he diagnosed himself to his mother. A friend in Indiana notified their health department, which notified New Jersey that this may be a case of monkeypox. Specimens were sent to CDC, who found them to be negative for monkeypox but positive for varicella. In the meantime, the

healthcare workers who saw the child asked for the smallpox vaccine and were offered it under the monkeypox IND protocol of informed consent. They chose to accept. Later that afternoon, they heard that the specimens were positive for varicella. The child is now doing well.

Summary: With an atypical case of chicken pox and knowledge that there could be person-person transmission indicated in the Africa data, and in the presence of a rapid response program and a useful vaccine, New Jersey chose to move ahead. One of the responders, who had been vaccinated in the earlier program, stated her satisfaction that she was immunized, since this was exactly the kind of case to which she had hoped she could contribute.

Interim CDC Guidance for Use of Smallpox Vaccine, Cidofovir and VIG for Prevention and Treatment in a Monkeypox Outbreak.
Presenter: Dr. Louisa Chapman, NIP.

CDC's interim guidelines on the use of vaccinia vaccine to treat monkeypox attempts to balance the risks of the smallpox vaccination with that of monkeypox exposure. The use of smallpox vaccinia vaccine for monkeypox is available under an IND sponsored by CDC.

The guidance was developed based on expert opinion and on the limited data from the African experience. The latter indicated a Case Fatality Ratio (CFRs) between 1%-10%, that rose with decreasing age. In 2003, in the U.S., one of the first 53 suspected cases, a 6-year old, developed encephalitis and 60% of the 20 confirmed cases were hospitalized.

Like smallpox, monkeypox is a DNA orthopox virus; they are 96.3% similar in the nucleotide sequence of their DNA. Pre-existing immunity to smallpox or vaccinia confers significant cross-protection, and pre-exposure smallpox vaccination prevents >85% of monkeypox. There are no direct data that post-exposure vaccination is efficacious, but indirect evidence suggests that post-exposure vaccination should prevent or ameliorate monkeypox disease as it does for smallpox. The incubation periods are similar (5-21 days) and CMI and anti-vaccinia antibody are detectable 8-10 days, respectively, after vaccination.

Assessments done included:
- The risk of secondary transmission of monkeypox in a household setting, ranging from 12-15% for unvaccinated contacts and 0.5%-1.5% in vaccinees. The risk of death from vaccinia is ~1-2 per million. That is substantially lower than the risk of monkeypox, which ranges from 7-15% in household settings and 1-3% in non-household settings.
- The risk of post-vaccinial encephalitis per million primary vaccinees (Lane et al, *JID*, 1970, 10-state survey) is of 1.5 per million adult vaccinees and somewhat higher for infants. The risk of life-threatening smallpox complications from vaccination and monkeypox fatalities both increase with decreasing age. As just reported, one of the initial confirmed monkeypox cases had encephalitis.

Conclusions were that:
- Pre-exposure smallpox vaccination is effective in preventing monkeypox infection and disease.
- Post-exposure smallpox vaccination is likely to prevent or ameliorate monkeypox.
- For close contacts, the benefits of vaccination exceed the risk.

CDC Interim Guidance was outlined:

- Contacts that confer risk: household and intimate contact, from airborne or contact exposure to droplets (>3 hours direct exposure within 6 feet or exposure to body fluids or lesions).
- Use of smallpox vaccine: Smallpox vaccination is the preferred prevention measure; there is no direct data on VIG (not demonstrated as effective in treatment or prophylaxis of humans) or Cidofovir for treatment of life-threatening infection.
- Investigators of human or animal cases should have been vaccinated in the last 3 years with confirmed takes, or be vaccinated preferably within 4 days of exposure. That guidance applies to healthcare workers as well, or they should at least be vaccinated within 2 weeks of exposure. Previously vaccinated contacts should consider revaccination within 2 weeks of the most recent exposure. State and local health departments should be contacted about exposures in child care, schools, health care, and other settings.
- Vaccination was advised for contacts within 4 days of direct physical contact with *sick* prairie dogs acquired since April 15 within the affected areas. Vaccination should be considered for similar exposure within 2 weeks.
- Since monkeypox is an environmentally hardy virus, vaccination should be considered within 4 days of initial direct contact for 3 hours or within 6 feet of a symptomatic case, or direct contact with respiratory secretions or contaminated surfaces (e.g., in veterinary care or other settings).
- Persons exposed to healthy prairie dogs or other healthy small mammals should not be vaccinated. Pre-exposure prophylaxis is not recommended for unexposed veterinarians and animal control workers, only the use of standard, contact, and airborne exposures prevention protocols. The exception is persons who may be involved in field investigations. The only animal known to be asymptomatically infected is the giant Gambian rat; all other animals should be sick, not healthy.

Contraindications to vaccination in the pre-event smallpox program

The risk of monkeypox disease is believed to be greater than the risk of adverse events from vaccinia exposure for most of those with contraindications in pre-event SVP. But before vaccinating them, the exposure should be assessed and confirmed by laboratory testing capable of detecting monkeypox, varicella and other rash viruses. Regardless of age, pregnancy, or history of eczema, vaccination should be done within 4 days of close or intimate contact with symptomatic confirmed monkeypox and should be considered within two weeks of recent exposure. Even for a person with active eczema, the monkeypox risk is more serious than the risk of smallpox vaccination.

However, smallpox vaccination is contraindicated for those with a severe immunodeficiency in T-cell function (e.g., HIV-infected adults with CD4 count <200 [or age appropriate equivalent], solid organ or bone marrow transplant recipients; those receiving high dose immunosuppressive therapy; persons with lymphosarcoma, hematological malignancies, or primary T-cell congenital immunodeficiencies). A life-threatening allergic reaction to latex is also a contraindication to smallpox vaccination.

Discussion included:

- This is a good example of how the SVP has helped public health staff to investigate other cases. New York has identified a vaccination gap among the veterinary staff called on to euthanize

or to do necropsy on contaminated samples. They have called on staff doing rabies specimens and who have no monkeypox contraindications and signed a contact with Cornell University for its catchment area. Use of the vaccine to ensure veterinary capacity is being debated. The current approach is to make them vaccine-eligible and to urge the exercise of standard precautions.

- Issues include pediatric use (assuming Dryvax® is used) and compensation. Congress is debating the latter. After close exposure, the guidance allows Dryvax® vaccination down to one day of age.
- Four to six states have vaccinated in this context, not many as yet, but it is occurring. Household contacts are being prioritized first, then work contacts, and issues related to animal exposures are begin examined.
- Dr. Dorothy Scott, of the FDA Office of Blood, expressed their willingness to work with CDC on the potential use of VIG, especially in the prevention of eczema vaccinatum.
- *How fast in the U.S. is lab confirmation of a case?* The guidelines advise consultation with the state health department about urgent consultation, and every state now is enabled by the Laboratory Information Network to have confirmation within a day. Most also have electron microcopy to identify orthopox viruses.
- *Were the healthcare workers in the hospitals that saw these patients vaccinated in 2002/03?* CDC does not know that yet but is seeking that information. But at least one hospital visited by Dr. Cono did not have vaccinated staff available, not even the infectious disease physicians.

Meningococcal Vaccine for Adolescents

Presenter: Dr. Paul Offit. At question: Should parents of adolescents be informed about the existence of meningococcal disease and the availability of a meningococcal vaccine?

Dr. Offit cited the question asked by the parents of a 12-year-old girl who died of serogroup C meningococcal infection within hours of illness onset: "Why didn't we know about a vaccine that might have prevented her death?" While the public health decisions are based on different considerations than those used to make individual decisions, a decision to not routinely recommend a vaccine affects the information available on which to base an individual decision. Meningococcal polysaccharide vaccine (MPV) is one example of this.

MPV is ineffective in the age group most at risk for meningococcal disease, infants and young children. It cannot help them because they cannot yet mount a good T-cell response, something a conjugate vaccine does not require. It also does not protect against serogroup B, which accounts for two-thirds of the cases in young children, but it does protect against A, C, Y, and W-135. Serogroup B is the only disease that is not immunogenic after immunization, and a meningococcal vaccine including serogroup B is not likely soon. MPV's induction of short-term immunity also requires booster doses every 3-5 years for young high-risk children who received MPV.

However, a meningococcal conjugate vaccine (MCV) of serogroup C is available in the U.K. It is likely to be licensed in the U.S. by 2005 and to replace MPV. It induces immunologic memory, obviating booster doses, and provides herd immunity, and protection against challenge.

MPV is not cost effective for any age group. For example, if given to all adolescents, it would cost ~$4 million to prevent one case and ~$48 million to prevent one death from meningococcus. Serogroup B accounts for most meningococcal infections in infants and young children. But 70-80% of the cases in adolescents and young adults are of serogroups Y, C and W-135. In young adults, MPV is immunogenic, safe, and about 85-100% effective against the meningococcal disease caused by the serogroups contained in the vaccine. It is the only vaccine currently available in the United States that protects against invasive meningococcal disease, and it does not interfere with MCV's capacity to induce immunologic memory.

Parents must decide whether they want to spend $80 to avoid the roughly 1:125,000 chance that their child would be infected with meningococcus, or the ~1:1,250,000 chance that their child would be permanently harmed by or die from the disease. But they are unlikely to hear about it to make that decision, for several reasons. Insurance coverage is unlikely for vaccines not recommended by CDC and AAP, which also makes it unlikely that clinicians will purchase, store, distribute, and educate about them. They also may assume that vaccines not routinely recommended have questions of safety and efficacy, rather than utility and cost-effectiveness.

Since the limited resources of CDC and state/local health departments must be directed against diseases that have the greatest health impact, the questions are:

1. Who should be responsible for educating parents about the consequences of meningococcal disease and the potential value of a meningococcal vaccine?
2. Should clinicians include information about the meningococcal vaccine together with information about routinely recommended vaccines to all parents?

Dr. Offit offered a suggestion that, at the time of the adolescent visit (~11 years old), parents be given an information sheet about this disease and the vaccine(s) available. He was unsure if this was a public health or an individual physician issue, but requested the committee's comments.

Discussion included:

- Dr. Abramson felt that this should be discussed at the fall meeting of the AAP's Committee on Infectious Diseases (COID). While he agreed that this gap should be addressed, he raised several issues: 1) this does not necessarily have to be done at the adolescent visit; it could be offered at any time after 2 years of age; 2) the issue of hyporesponsiveness to repeated vaccinations (a response to dose one is greater than dose two) requires a literature search; 3) the college age is the second highest time of risk; and 4) while the conjugated vaccine will be welcome, it will create another two-tier system. The parents who can afford it may decide to get it, versus those who cannot. Insurance companies do not pay for it.
- Dr. Offit rebutted that there are no data on hyporesponsiveness to indicate that it is a clinically relevant factor; there already is a two-tier system; and information should not be withheld due to that.
- Dr. Katz reported that North Carolina requires college parents to be informed about the meningococcal vaccine and to sign a waiver if they do not want it, a policy that raised coverage from 66% to 82%. Such legislation is pending in a number of other states.
- Dr. Phil Hosbach, of Aventis Pasteur could not say when the conjugate vaccine would be licensed, but the application will be submitted this year. The approach to target groups will be phased, first to adolescents, then to toddlers and then to infants.

- Dr. Baker was concerned about but resigned to the fact that federal and state programs have already created a two tier system. To not offer education is not an option. And, while there may be issues about vaccine tolerance at ages 2-5, there are none related to the adolescent period, which goes to age 21.
- However, the cost of this to communities in terms of expense and resources, if there is only one case, can be significant when the media picks this up. For example, New York just legislated a summer camp as well as college waiver requirement, when a single child died of meningitis in a camp. This was clearly not a science-based decision.
- In the U.K., group C went from being fairly common to virtually having disappeared since they introduced conjugate vaccine to age 18 and then extended it to age 25. The carriage rate has dropped 66% from the pre-immunization period. Clearly, a herd effect benefits even those unvaccinated. The vaccine introduction was cost effective. And all the immunization materials, from birth on, describe meningococcal symptoms and the steps to take. Evidence of hyporesponsiveness was seen to subsequent doses of the polysaccharide in college students, but that was reversed with the conjugate.
- Dr. Nancy Rosenstein, of CDC's Meningococcal Branch, recalled the 4-5 years since ACIP recommended a general awareness program of meningococcal disease and vaccination for college students due to clearly elevated risk. The polysaccharide is 85% effective and prevents 70% of cases, and cases have decreased for serogroups Y and B. But, while the wording clearly tasked health department and clinicians to advise this, the Branch has also heard a lot of frustration from colleges and physicians at a lack of clear guidance on whether or not to vaccinate.
- Dr. Decker reported that Aventis immunizes their production workers every 3 years. Although the antibody concentrations drop, they maintain protective levels. He also expected both Aventis and GSK to have adolescent acellular pertussis vaccines licensed in the next two years; Merck is progressing with an HPV vaccine, and GSK is also working on a herpes simplex vaccine. All are focused on adolescents. He was unsure that the field will be prepared to implement those new vaccines unless preparation begins now.
- Dr. Deborah Wexler stated the Immunization Action Coalition's agreement that there is a deficit of information about the vaccines that are not recommended for children, teenagers and adults. The IAC is developing material on such vaccines in the coming months and advises discussion with patients' health professionals about it.
- Aventis will pursue a vaccine for infants, but is first pursuing the more rapid licensing possible for a polysaccharide vaccine with established efficacy. A vaccine used among infants requires much more data.
- Mr. Jim Turner of American College Health stated their support of informing parents as much as possible. Even before the ACIP recommendation, they were moderately successful in increasing meningococcal vaccine uptake. But uptake did not really rise until the ACIP statement, even a permissive one. He urged ACIP to make a statement on the need to issue information.
- Dr. Jackson cited this discussion as an example of the fact that more public engagement is needed in policy decision making.
- Dr. Naus cited increased group C outbreaks in Canada before the conjugate was released, mainly among 5-19 year-olds, but also among young adults in their twenties. When the routine universal immunization began with the group C licensure to late adolescence, they found incremental benefits to age 15-16 over the polysaccharide vaccine in terms of effectiveness and protection against group C disease. Meningococcal disease is greatly feared by parents, with a fulminate course that is higher profile than, for example, pneumococcal disease. That

vaccine was funded even before pneumococcal vaccine in some districts. Canada also has a two-tiered system, so pediatricians are increasingly asking if they can inform the parents about recently licensed vaccines not yet publicly funded. There is some perception that until the government pays for it, it is not worth doing; some public health departments are also reluctant to provide vaccines that people have to pay for. The Canadian National Advisory Committee on Immunization is trying to change that in view of the several-year gap that funding entails.

Public Comment

Ms. Leslie Meigs, age 12, of Houston, Texas, is a member of the Meningitis Angels organization, a patient/family support group. She urged that more information on meningococcal meningitis be distributed and related her own experience with the disease. She was hospitalized for two months at age 8 with meningococcus and incurred a hospitalization bill of >$500,000. The insurance program that covered her was dropped the next year. She was given an IND drug that put her in a coma, but left her eyes open and, despite frequent drops, resulted in scars. She developed bedsores despite being in a computerized bed that moved her and her kidneys stopped functioning, requiring catheterization. She had surgery after her release to remove the hard portion of her scars, and needed dialysis for two months. Her kidneys are still not fully operational. After the double blind study, she learned that she had received the IND rather than the placebo, and she was the only child who left the hospital with fingertips and toes. She urged the committee to promote the vaccine as much as possible.

Nancy Springer, from New York, has a son named Nick, who is a quadruple amputee from meningococcemia that he contracted in a summer camp. She suspected that he contracted it when he shared a water bottle. She first knew of meningococcemia when her son was on kidney dialysis and life support, and receiving the last rites of his church. She has done everything possible in New York to promote vaccination without promoting a panic. The problem is that adolescents share things all the time: lip balm, water bottles, etc. Education of the parents is the key.

Susan Koenig is the mother of Emily Grace Koenig, who died at age 12 of meningococcal septicemia. Mrs. Koenig and her husband Al drove 13 hours from Coatesville, PA, to attend this meeting, in order to do all they can to prevent other parents from losing their child. Emily attended a full day of school the day before she died, did her homework and went to bed. She had cold symptoms, took a cold medicine and vomited overnight. The next day she seemed to have a stomach virus, for which the family doctor advised rest and fluids. By mid-afternoon, she had diarrhea. Upon bathing, she noticed a bruise and her legs started to ache. They had no idea that this was a sign of septicemia. By that evening, her eyes were bloodshot and her delirium began. She stopped breathing on the way to the hospital, where they began life support immediately. In critical condition, she died within two hours of arrival. Nothing could be done. Mrs. Koenig wanted to know why the public is so inadequately informed of the symptoms and dangers of this disease; why the doctor did not warn them; and why they did not know about an 85% safe/effective vaccine that has been available for 20 years. Every person and provider has a right to know about this disease and the currently available vaccine. That knowledge would make a significant difference to avert a lifetime of devastation that extends to family , school, and communities. She urged the ACIP to help save lives by promoting knowledge of this disease and vaccine in the U.S.

Mr. Koenig commented that meningitis plays Russian roulette with children. Emily contracted it from a woman who sneezed on her, who turned out to be a carrier. can infect. He urged the committee to remember to stress in any material developed the terribly random nature of the disease, such that a person can be infected from a droplet.

The committee was in **consensus to develop a supplemental statement on meningococcal disease to encourage healthcare providers to educate parents both about the disease and the vaccine available to prevent it**. When the meningococcal statement is revised in the next 2-3 years, that will be incorporated into that statement. Dr. Baker was pleased at this, and urged assurance that the ACIP and AAP statements' text be compatible. Dr. Abramson urged the vaccine's use for all ages, not just adolescence.

Dr. Rosenstein expected, with a conjugate vaccine likely in the next two years, that development of the ACIP statement will be complicated. She suggested forming a workgroup on the statement and its recommendations. Dr. Salisbury offered to share with the NIP the U.K.'s multiple information materials for parents and youth., all fully tested with target audiences. For example, all the materials for parents tell them how to do a glass test if they see what they think might be a meningococcal hemorrhagic rash.

Development of High Workload Disposable Cartridge Jet Injectors (DCJI) for Mass Vaccination Campaigns.

Background. Presenter: Dr. Bruce Weniger, NIP.

Multi-use nozzle jet injectors (MUNJI) have delivered billions of doses since the 1950s in mass vaccination campaigns. They are capable of delivering 600-1,000 injections/hour.

However, safety concerns for MUNJIs have emerged since a mid-1980s outbreak of hepatitis B in a California weight loss clinic. The jet injector was found to be contaminated with hepatitis B, and testing revealed that it would remain even if swabbed. In the early 1990s, field studies detected blood from the previous injection in a quantity that could easily transmit hepatitis B. Animal and human tests found blood in about 100 samples of all five of the injection devices tested. The WHO and CDC/ACIP recommended against their use until they were proven safe. The manufacturer removed them from the market after their largest customer, DoD, dropped their use, and due to liability concerns. Despite attempts to re-engineer them with safety caps and other devices, regulatory worry lingers, including about what would constitute an acceptable risk. Currently, there is no licensed high-speed vaccination device of unquestioned safety. NIP has worked to develop disposable cartridge jet injectors (DCJI – "dickjees") with several companies, budgeted at ~$3 million. Safe, high-speed vaccination will be needed for epidemic response and perhaps bioterrorism response.

DCI, Inc. Presentation. Presenter: Ms. Linda D'Antonio, Vice President of DCI, Inc.,

DCI, Inc., is NIP's contractor for this work. Information from their Phase II project for their injection system, LectraJet HS ("High Speed") was presented. This needle-free injection system

for mass immunization campaigns has developed since 1997 with CDC's design/performance specifications:

- Safety: disposable, single-use, auto-disabling cartridges, allowing a clean, fingers-free end-user filling of the cartridges with vaccine as well as vaccine manufacturer prefilling; fingers-free loading/ejection of the cartridges; all sterile components provided to avoid any field sterilization requirements; no sharps waste; reduce volume of medical waste; and interlocking mechanism to prevent unintended firing.
- Speed: rate of >600 injections/hour or 10/minute.
- Cost: competitive to disposable syringes, which this system is intended to replace.

Proof of principle studies were outlined which demonstrated the injector's capability in *in vivo* studies and through prototypes. Photographs were shown of its use, demonstrated in piglets, fat, and muscle. The injector's components were also outlined: a case (which will have legs for ease of use in the field), cartridges (low cost at high volumes, of ~6-9 cents/cartridge), the hand piece that delivers the injection (800 injections manually, or 3,000 with a battery powered motor, per charge), and a magazine (that holds/manages the sterile cartridges). The magazines can be disposable or reusable and have filling stations to allow clean and quick filling of cartridges with vaccine through an orifice. There are two options for the latter: a syringe (to reconstitute vaccine) which can be inserted in the cartridge filling station; and the prefilled vial-to-cartridge filling station. Both prevent dose wastage.

Discussion included:

- *The old injectors burned if not applied at proper angle; do these?* With slow-speed devices, the patient's arm has to be completely immobilized, or the injection can take a third longer and can cause a laceration. This new cartridge has a gripping surface to prevent the arm's movement.
- *What is the accuracy of filling the vials with small volumes?* DCI was asked to begin with a volume of .05 ml to be ready for use for measles. But the system is capable of lesser amounts; the volume depends on the plunger's stopping point. *Are there multidose vials?* Yes, overseas those are used for measles campaigns. But when the military dropped their injectors' use in 1997, the 50-dose vials of yellow fever, meningococcal, and pneumococcal vaccines produced by Aventis were taken off the market. They could return if these systems return.
- *What is the depth of the injection?* The original contract was for a measles application in a subcutaneous injection. But part of the research is to deliver IM injections as well, which has been tested in the piglets. DCI is confident that they will be able to accomplish either subcutaneous or IM injection, simply by changing the size of the orifice.

Update: Evaluation of Non-Thimerosal Containing Vaccines in Non-Human Primate Model

Presenter: Dr. Polly Sagar, NIAID, Division of Microbiology and Infectious Diseases

The committee was updated on NIAID's ongoing primate clinical trial. It follows up on a preliminary clinical trial on the distribution of thimerosal excretion by infants. The original study explored whether the guidelines developed for methyl mercury (MeHg) were appropriate for assessing the safety of thimerosal, and how the distribution, metabolism, and excretion of

thimerosal and methyl mercury were related. The results could have been that they are 1) equivalent; 2) similar, but methyl mercury guidelines are for either an additional or lesser margin of safety; or 3) they significantly differ in distribution, metabolism and excretion.

Thimerosal is ethyl mercury thiosalicylate delivered normally in an IM injection with spaced intermittent exposure. Methyl mercury is found primarily in food. Its exposure guidelines are based on oral intake with continuing exposure and a steady state distribution. They primarily focus on maternal and fetal exposure, while thimerosal concerns focus on infant vaccines. The mercury guidelines extrapolate models of fetal exposure effects from measurements made of maternal hair, while thimerosal exposures from vaccine are known.

Clinical study. Dr. Sagar outlined a clinical study done at the University of Rochester. It involved infants aged 2 or 6 months who received their scheduled vaccines which, at the time, normally contained thimerosal. Blood, urine and stool samples taken supported the conclusion that the blood half-life of thimerosal was considerably shorter (6-8 days) than that of methyl mercury found in adults (20-30 days). They also found that the infants excreted a significant amount of mercury in the stool, something not seen in the animal model until after they were weaned; and it reduced with the animal's growth, including into their hair.

Animal study. A study in infant macaques was done by the University of Washington, with mercury lab analysis again done at the University of Rochester. This study examined the amount of mercury in the typical infant vaccination schedule and immunized infant macaques with thimerosal-free vaccines for their first three weeks (1 week equated to one human month), or oral methyl mercury at a dose of 20 μg/kg, or were given vaccine with thimerosal at an equivalent 20 μg/kg dose in the form of thimerosal. They received a total of 80 μg/kg over four vaccinations. Equivalencies were charted for body weights during the dosing periods and at time of sacrifice, brain weights and ratio of brain to body weight. Data on a few more animals will be added soon, but most of the data are in.

The levels of methyl mercury in blood rose after each injection but dropped over the following week, but there was a rise over time that peaked at about 15 ng/ml after the fourth injection. For thimerosal, the peak level was ~50 ng/ml despite equivalent mercury doses, and the blood levels dropped quickly after the last immunization. Data modeled for methyl mercury indicated the distribution of methyl mercury beyond the fluid compartment, to be also protein-bound, and rapid uptake and distribution after the oral dose. The overall half life in blood is ~23 days for methyl mercury, with a clearance at ~23 days. For thimerosal, the distribution was about the same, also protein bound. After an initial large variation in distribution after IM injection, they rose to much the same level, but the half life in blood was ~4.5 days and clearance was significantly higher.

The washout period after exposure for methyl mercury, comparing blood and brain at time of sacrifice, showed a terminal half-life clearance in blood of ~24 days, and ~59 days for the brain. This is consistent with the literature for adult animals in other studies. The peak levels in brain were ~120 ng/gm and ~40 ng/ml in the blood. The term half-life for thimerosal in blood for clearance was ~3.7 days and 17.6 in the brain. The extrapolated brain peak levels were ~42 ng/gm and ~20 ng/ml for blood.

The compared half-lives, based on the one-compartment model, were ~23 days for methyl mercury and ~5 days for thimerosal, consistent with what was seen in the clinical trial for children. The washout from blood was ~20 days for methyl mercury and ~4 for thimerosal. The half life for washout from brain was 59 compared to 18, and the blood-to-brain ratio was consistent for thimerosal and methyl mercury.

The conclusions were that:

- The initial absorption distribution for oral methyl Hg and thimerosal ethyl Hg delivered IM are similar.
- Blood mercury derived from thimerosal has a much shorter elimination half-life compared to methyl mercury.
- There is minimal accumulation of total mercury during the IM injections of thimerosal, while there is continued accumulation in blood during the oral dose of methyl mercury.
- There is a similar blood-to-brain partition for methyl mercury and ethyl mercury.

Discussion included:

- *What was the animals' baseline of mercury levels before the first dose?* Analysis was done of the mother's food, the infant's formula, the water, and samples from autopsy material from other animals in the colony. All had mercury at or below levels of detection.
- *Which is more important in mercury toxicity, the peak or exposure over time?* Opinion varies. Some studies indicate exposure over time, others suggest that if it occurs over time but sporadically with peaks, that may be important too.
- *These are useful data to have, but they do not tell much about the likely mechanisms of toxicity. Were these animals dosed with thimerosal, or ethyl mercury?* Thimerosal, to expose them to 20 µg/kg of ethyl mercury. *The key question is whether there is any additive effect, but these animal models could not show that since they were sacrificed.* Correct; that was the only way this study could match brain-to-blood levels. The University of Washington's neurodevelopment and behavioral groups observed and evaluated the animals, but this was not designed to be a toxicity study, but a pharmacokinetic study to assess exposure. Now that that is done, toxicity will likely be studied.
- Dr. Chen advised the committee that, pursuant to the screening results of the VSD analysis, a follow-up study is being done of randomly selected children. A 3-hour standardized battery of neurodevelopmental assessments will be done by trained psychologists blinded to thimerosal exposure.

Public Comment

Ms. Lynn Redwood, of Safe Minds, appreciated any data on ethyl mercury, and asked if the blood/brain levels measured were of organic or inorganic mercury. Dr. Sagar said they were measures of total mercury; when they began, there was no assay to distinguish between ethyl and methyl mercury. But work is being done on that and NIH is saving the material for those analyses. Ms. Redwood asked if the vaccines used also had aluminum, which may involve a synergy of the metals and competition for excretion. Dr. Sagar did not know specifically; the vaccines were procured from a local pharmacy. She would have information on the exact lots used, but not at this meeting.

Ms. Redwood again appreciated the data, but commented that it may not exactly typify real life. Infants are born pre-exposed to mercury, according to NHANES. It is possible to model prenatal exposures in an infant monkey and then add to that the post-natal exposures. Dr. Sagar agreed that this could be done, but this first study emphasized the basics. There are a number of very interesting research question that can follow.

Dr. Plotkin added that this study demonstrated that ethyl and methyl mercury are not the same, a significant finding that "should not be lost in peripheral questions."

Dr. Modlin had to depart for the airport during the lunch hour, and Dr. Levin acted as Chair on his behalf for the balance of the meeting.

Enhancing Public Participation in Immunization Decision Making
Presenter: Dr. Roger Bernier, NIP

This project was part of a special CDC assignment to Dr. Bernier in October 2001, to explore how the immunization community might enhance public engagement in decision making about vaccines. The concept was developed at the Wingspread conference held in 2002 with the assistance of a contractor, the Keystone Center. Dr. Bernier publicly acknowledged the contribution of Keystone's Ms. Mary Davis Hamlin, who also attended this meeting, to the project.

Different levels of public participation can inform the public (one-way), consult with the public (minimal involvement), and collaboration (bidirectional). Public health is not well prepared to operate at the latter end of the spectrum. Engagement of the public is of value because it is the right thing to do in a democratic society; people should have input to the decisions affecting their lives; it is the best thing to do to develop good solutions; and it earns more support for the final decision. To accomplish these things, trust-building activities are needed.

The organizational planning group formed at Wingspread included health professionals, minority groups, government agencies, and representatives of the "critical", neutral, and general public. A post-conference planning group was formed, again with stakeholder groups (academia, industry, government agencies, non-governmental organizations). They developed a collaborative problem-solving process to arrive at optimal solutions to problems presented up-front. Meeting over time, they drafted a proposal for a demonstration project of this enhanced process. The proposed name for this project was the Vaccine Policy Analysis Collaborative (VPAC). NVAC was the first group to which this was presented.

Dr. Bernier outlined the other options considered:
1. An IOM roundtable alone (problem; this would lack the desired linkage)
2. NVAC implementation alone, but with a neutral contractor (Keystone, Rand, etc.)
3. An NVAC/IOM joint implementation with IOM roundtable members appointed first and then NVAC selection of workgroup members from that group
4. The option proposed, the key features of which were participation of stakeholder groups of the organized and general public; providing a "safe harbor" environment to foster candid discussion and a "not strictly partisan" work ethic. Activities would include dialogue, analyses of pending decisions and tracking. The agenda will depend on the decisions faced by the government. In

consultation with stakeholders, a list of options with pros and cons would be drafted about how the decisions could be made. This group would make no recommendations, only inform the decisions of existing formal groups.

5. NVAC evaluates for itself whether/how to enhance pubic engagement. Industry felt it could only support that option, and withdrew when its was not selected as the desired option. But Dr. Bernier felt this was not mutually exclusive; NVAC could still be so involved as well as the option proposed.

The kinds of issues likely to be addressed involve values as well as technical aspects, cross-cutting and implementation issues. Linkages would be suggested for the government's consideration and response. Funding of the would be mixed if possible, through a foundation (e.g., the CDC Foundation). The demonstration project term would be three years, with the goal of a better decision-making solution-finding process.

The potential questions for VPAC to address are would be those for which a decision has truly not yet been made, where the decision not urgent, and where it involves values as well as facts. The government would really want input to its inform decisions, and would not just be consulting for its own sake. Examples could be: 1) should doctors oust children from their practice if parents refuse vaccination?; 2) should philosophical exemptions to school laws be available in all states?; 3) should the rotavirus vaccine be reintroduced into the US?; and 4) should we require less proof of causality for awards in the Vaccine Injury Compensation Program?

VPAC's organizational structure was extensively discussed by the group. A mechanism was needed to carry out the key functions in dialogue, information gathering and interpretation, and report writing. While existing mechanisms could quickly implement the project, the structure also required flexibility to deal with enhanced public engagement rather than "business as usual". Two existing mechanisms meeting these criteria were identified, federal advisory committee workgroups and IOM round tables. Both are working level, pre-policy, information-exchanging groups that are relatively free of regulation.

To provide the proper balance of independence and support, the planning group proposed a joint/simultaneous structure of an NVAC workgroup, the members of which would also serve on an IOM roundtable. A neutral contractor would work by consensus with NVAC and the Wingspread steering group to appoint the NVAC workgroup members and the IOM in turn would appoint them to an IOM Roundtable. Both would function normally: the roundtable as the research arm of the workgroup, and the NVAC workgroup members responsible to write the report. (IOM roundtables are not allowed to do so).

To begin, the federal government, through NVAC, would identify pending decisions to be considered in the next six months. Outreach would be done for the general public's judgement on the question, after which VPAC would do the analyses and the NVAC workgroup would write the report, probably including a list of options. The government then would give feedback to the VPAC, which could track the product of its work. But to begin, a linkage or gateway to government agencies would be needed. Presentations such as this are still being made to the immunization community (e.g., ACIP, NVAC, ASTHO).

To date, the enhanced method of engaging the public in immunization issues has been designed with six major interest groups. The proposal meets the interests and is supported by most of the stakeholders, but does not meet the interests of some industry and pro-vaccine advocates who participate in most of the process. Most of the objections have been about procedural aspects of the planning process, but some relate to the design of the enhanced proposal. The group has attempted to replace and retain the stakeholders' participation as possible. All are welcome to return to the process, as are others with a mutual interest who have not yet participated. The goal is to remain intact as a planning group and to advocate for this proposal until it can be adopted and implemented.

The key messages about VPAC were:

1. This offers potentially large benefits: enhanced citizen/stakeholder voice/role, to help pursue better solution options, more ownership/support of decisions; increased trust.
2. The potential risks are low: this is not a new activity, but an enhancement of public engagement; it is not a new committee and it makes no recommendations. There is no commitment to a permanent change, it is just a time-limited demonstration project of these ideas that can be retired if it does not meet needs. It enhances capacity without supplanting other current public engagement tools – it is not mutually exclusive to other activities; and the structure makes it unlikely that any one group will dominate. So, the benefits are worth having and the risks are worth taking.
3. This would not be the first such undertaking. Other organizations pursuing a similar path of engagement are the American Association for the Advancement of Science (AAAS), which is forming a new Center for Public Engagement in Science; the Royal Society has begun a new 5-year Science in Society program; and the Organization for Economic Cooperation and Development (OECD), which has the world's key democracies as members, has published a new handbook "Citizens as Partners". The EPA announced a new agency-wide Public Involvement Policy in May 2003; and Health Canada's Health Products and Food Branch (similar to the FDA) formed a new Office of Consumer and Public Involvement.
4. Upon a recent similar presentation, NVAC expressed support for the effort to enhance public participation, but expressed concerns about the need to share the workload with the IOM and others. They decided to form a workgroup to recommend to NVAC about public participation in general and VPAC in particular.

Discussion included:

- Dr. Decker stated NVAC's strong feeling that this activity belongs to its mission. He appreciated the work of Dr. Bernier and the group to develop it to this point, but felt that the proper action now is for NVAC to explore how to give this a proper home. He commented that "PAC" may sound like an official advisory group and thought that, once integrated into NVAC, that acronym may not remain.
- Dr. Plotkin stated the vaccine industry's agreement with the principle of public involvement and that NVAC is its proper home. He advised that this activity focus on NVAC itself, rather than complicating or slowing matters by involving another organization. He thought that the principle criticism of doing this through NVAC was that some stakeholders are unhappy with NVAC. He thought that not a good reason to fail to use what appears to be the most appropriate group to obtain public input.
- *Would this be another resource like the IOM, but one offered as a resource to a number of advisory committees?* Yes, it would be a standing group that could supplement and complement existing committees to aid their analyses of issues they address.

- *What are the specific objections to this, and how would the linkage to public input come about?* Discussions are under way with many outside of the immunization community who have developed many innovative techniques to obtain the input of Americans on a number of issues (e.g., America Speaks, the Kettering Institute of Ohio, etc.). Much can be learned from them, but the focus to date has been on the stakeholder aspect. The objections included concerns that certain interest groups might dominate the proceedings (e.g., anti-vaccine or vaccine critics). But the project design greatly lowers that risk with six different constituencies groups represented. And, regarding this task belonging primarily to NVAC, the planning group's feeling was that the outreach to the IOM and perhaps others was necessary to build the trust of the analyses that VPAC would do. Dr. Bernier commented that he still gets e-mails three years later that people cannot accept that MMR does not cause autism. The involvement of a clearly independent group can only help.
- Dr. Decker said that incorporation into a well-organized, well-established group such as NVAC was in part to avoid having an "advisory group" to offer its opinion willy-nilly to whatever group. Dr. Bernier reiterated that creating any competing centers was not the intent. VPAC would use existing structures to help them to do a better job by providing an opportunity to gather input.
- Dr. Wexler, who was at the Wingspread conference, termed it contentious. She and another pro-immunization advocacy group representative left early, feeling that the process was pre-conceived rather than developed by consensus. Vaccine critics had a dominant voice, being five of the 30 at the initial meeting. She was concerned that this group would not represent the real public to know their vaccine concerns.
- However, Dr. Jackson was also at Wingspread, and had different impression. He described ample opportunity to present and discuss feelings about developing such a body. The ideas crystallized as the process went along, and he thought some who left did so unfairly and without adequately indicating why.
- Dr. Lou Cooper, of the National Network for Immunization Information, also had a different experience than Dr. Wexler, who left before he arrived. He described an open and respectful dialog and an experience that reinforced for all how important public engagement is. One of his assignments was to explore with existing federal committees and their Chairs their views of how their committee functioned, particularly as related to public engagement. Upon reflection, each said that their mission had room to engage the public. Regardless of the methodology used, it is important to do so.

Adult Immunization Workgroup Update
Presenter: Dr. Zimmerman.

A few changes were made to the adult immunization schedule:
- Schedule and footnote titles were revised to be more readable, delineating the recommended schedule of adult immunizations by age group and by conditions
- Repetitive and redundant notes on the bars were deleted.
- The pneumococcal polysaccharide vaccine schedule was revised to reduce the potential for confusion about when revaccination is needed.
- Special note H on medical conditions was revised to suggest consideration of administering Hib vaccine..

- Footnotes were revised on: 1) Td: clarified that pregnant women can receive it and added an *MMWR* reference about using Td as prophylaxis for wound management; 2) rubella: added *MMWR* reference on avoiding pregnancy for 4 weeks, not 3 months); and 3) varicella: added a recommendation for those "who may be at high risk for exposure or transmission of VZV."
- Dr. Zimmerman also suggested adding to the influenza footnote that "LAIV is available as an option for vaccination of healthy persons aged 5-49 years."

An *MMWR* Notice to Readers on the schedule update will be published this October during Adult Immunization Awareness Week. It will highlight the challenges to meeting the HP 2010 targets for influenza and pneumococcal vaccination, the use of facility- or practice-specific strategies (e.g. standing orders), the reduction of missed opportunities, and additional resources available at the CDC Website and state health departments.

To meet the HP2010 challenges for pneumococcal vaccination, increases will be needed of 51.2% for those aged 18-64 and 36% for those aged ≥65 years. For influenza vaccine, increases of 43.6% are needed for those aged 18-49; 23.7% for those 50-64; and 23.6% for those ≥65 years.
In other activities, the University of Michigan is gathering data to assess the usability of the adult schedule to the practicing physician. That will be reported in 10/03.

Discussion included:
- *In the varicella change, how is high risk for exposure or transmission of VZV defined?* The original footnote is unchanged and does that: healthcare workers, family contacts of those immunocompromised, teachers, daycare workers, hospital residents/staff, etc.
- *What is the status of the pneumococcal polysaccharide vaccine? Is there only one manufacturer now?* Wyeth withdrew from the market, leaving Merck. Dr. Tom Vernon of Merck stated that, based on historical demand, there will be enough Pneumovax® vaccine to meet market demands and perhaps even an increase.

Vote:
Dr. Tompkins moved to accept the revisions as recommended, and Dr. Hanson seconded the motion.

In favor: Birkhead, Brooks DeSeda, Gilsdorf, Finger, Hanson, Levin, Tompkins, Zimmerman.
Opposed: None
Abstained: None

The motion passed unanimously.

Update of the Harmonized Schedule Workgroup
Presenter: Dr. Greg Wallace, NIP

Dr. Wallace outlined several issues of the childhood/adolescent schedule for the ACIP's guidance, focusing on the harmonized and catch-up schedules. The 2003 childhood/adolescent schedules:

- Added a sentence to DTaP, Hib, and PCV to indicate timing of the last dose.
- Added a footnote reference to Hib dose #3 to indicate that no 6-month dose is needed for Pedvax, Hib or Comvax. The footnote for influenza will be updated to incorporate FluMist®.

He asked the ACIP's guidance on several items related to three draft schedules presented (A, B, and C). The formal schedules will be presented for a vote at the October meeting. The adolescent Td bar, which extends from 11-18 years, was extended last year from 16 to 18 when the Td vaccine shortage ended. It was extended down to 11 years (from 14) to emphasize the adolescent dose.

At question: whether to continue with the orange (recommended) bar from 11-18 years (option A), or split it to 11-12 years and then a green catch-up at 13-18 years (Option B); or to begin the green bar at 16 years old.

Discussion included:

- In view of the question of how many 17-18 year-olds will actually come in, some members preferred to keep the historic 11-16 bar and having catch-up at 17-18 (Option B with TD 11-16 in the yellow).
- The opportunity presented by a pre-college visit by a 17 or18 year-old might support keeping the broader width of the bar, as well as other opportunities.
- Dr. Marty Wasserman, of GSK, is a pediatrician and former state health commissioner. He suggested making a recommendation for 11-12 year-olds coming in five years after the primary series, and then having a catch-up or review from ages 13-18. This would help pediatricians seek an early pre-adolescent spirit.
- The schedule C with green Hib and IPV bars is busy; that much green risks losing the emphasis on catch-up. A preference for B as a whole was expressed.

The 1996 recommendations for an adolescent dose of Td clearly indicated 11-12 as the recommended time of vaccination, which would put the catch-up bar at 13-18 where it is. That is the ACIP policy.

Placement of catch-up bars: The workgroup was split on whether catch-up should be highlighted only for special attention or for vaccines. Again, the ACIP expressed a preference for schedule B and not C, as regards Hib and IPV.

General format of the catch-up schedule: The format is two different tables divided by age through 6 years and 7-18 years, with one set of footnotes. This was approved by ACIP in 2002. Three different editors sent this back with three different versions. The *MMWR* version had two tables with two sets of footnotes. The workgroup wanted consistency of the table used between the agencies, preferably with one footnote. There was no disagreement by the ACIP members to that.

Agency/Committee Updates

DOD. Dr. Diniega reported that active duty personnel are required to have influenza vaccination, requiring ~3 million doses per year. Their lab surveillance received 3100 specimens

from DoD facilities, of which 41% were positive for respiratory virus. Of those, 23% were positive to influenza A, 24% were influenza B, 42% were adenovirus, and 115 were others. The outpatient surveillance indicated ILI at an average of 10% of all visits. A good deal of adenovirus is seen during basic training. Barr Pharmaceuticals was contracted in 1991 to develop an adenovirus vaccine for DoD (Types 1 and 7). FDA approval is expected in 2006.

The policy to vaccinate all recruits against hepatitis B passed last year is now fully implemented across all services. Of the ~300,000 recruits trained annually, about a third are positive for anti-HBsAg, and that is without the serological screening programs fully implemented as yet. All recruits have been vaccinated for meningococcal disease for several years with the quadravalent vaccine. The anthrax vaccination program had slowed down, after delivering ~4 million doses to ~1 million personnel. The DoD pandemic influenza response plan was put into staffing in the beginning of June, and the final approved plan is expected in September. Finally, at this, his last meeting, he expressed his pleasure to have been DoD's ex-officio representative. He thanked the ACIP and CDC for all their advice and support given to both the national vaccination program and the DoD vaccination plan.

FDA. Dr. Baylor had left, but licensure of FluMist® had already been discussed.

NIH. Dr. Heilman had left the meeting; there was no NIH report.

NVPO. Dr. Ben Schwartz spoke for NVPO Director Dr. Bruce Gellin, who was at a SARS meeting in Malaysia.

- The NVPO office is moving to Washington, D.C.
- NVPO has been charged to complete the pandemic influenza preparedness and response plan by the end of July and to identify resource needs for the FY05 budget. The plan's structure encompasses a core plan (objectives and guidelines for national decision making, legal authorities, and a summary of all the components of pandemic influenza preparedness and response); that is followed by planning guides for state/local health departments and healthcare systems, as well as technical annexes on influenza disease and pandemics, surveillance, vaccine development/production, vaccination strategies, antiviral drug strategies, communication, research; and lessons from swine flu and other mass vaccination/preparedness programs. This activity has to be done before the next ACIP, but he welcomed any review of the draft plan (to be completed by the second week of July) to be incorporated by the third week.
- The Vaccine Supply Report recommendations from NVAC were completed and included recommendations for: increased funding for stockpiles, increased support for CBER FDA to enhance its ability to review products; a strengthened VICP; a requirement for manufacturers to notify HHS if they plan to withdraw from the market; increased information about vaccine supply for providers and the public; launching a campaign to emphasize the safety, efficacy, and benefits of vaccines; convening a group to evaluate appropriate incentives for manufacturers to sustain supply and stimulate development of new vaccines; and streamlining/strengthening the regulatory process.
- The ACIP members were invited to two Future Vaccines meetings planned to be held in Washington, D.C.: August 8-10, 2003, on pneumococcal disease prevention in adults and potential vaccine strategies, and on March 3-5, 2004, one on vaccination of newborns.

NCID. Dr. Alison Mawle reported that the NVAC polio lab containment interim survey, which is housed in NCID, had been ongoing for over a year. A third survey to non-responders was to be sent out this week. NVAC created up an oversight committee, chaired by Dr. Ann Arvin, that will validate NCID's survey. That committee may report to NVAC in February. When polio is eradicated, the final survey will be done again, when lab containment measures are implemented.

VICP. Dr. Geoffrey Evans updated the ACIP on the number of claims filed. So far in FY03, 1760 claims have been filed (over 8 months) and 957 for FY 2002 (more than four times the number the previous FY). The vast majority allege thimerosal-related injury. For the "new" vaccines, DTaP has now been given for the fourth and fifth dose for >10 years and the primary series has been given for >5 years. Still, only 114 injury claims have been filed. There is one remaining pre-1988 claim left. The average time for adjudication (excluding thimerosal litigation) is 3 years. Claims awarded total $1.4 -1.5 million/year, and the Trust Fund balance is $1.8 billion. Annual revenues are $150 million to $200 million.

Thimerosal litigation in the civil sector includes 250 individual and class action (15) suits against vaccine manufacturers and administrators (physicians). These actions are of three types: 1) the traditional tort claim for a specific child injured, seeking lifetime care; 2) the class action "medical monitoring" claim for currently healthy persons seeking future monitoring/compensation from any vaccine-related injury; and 3) derivative/third party claims by parents/guardians claiming their own injury aside from the child injured (e.g, for loss of companionship, etc.).

The National Vaccine Injury Compensation Act (NVICA) requires petitioners to file first with the VICP unless there is an adulterant/contaminant in the vaccine. They are trying to get around that to go into the tort system first, based on two arguments: 1) they are not suing for "vaccine-related injuries since they allege that the vaccine contains an "adulterant" or a "contaminant", and 2) the medical monitoring claims are for <$1,000.

As it happens, the VICP does not handle class action suits or third party claims, so when state/federal courts reached preliminary decisions as to whether the suits should stay in civil court to go into the VICP, the decisions have been mixed. The cases for individuals were sent to the VICP, since thimerosal is not an adulterant. But the class action and the third party suits not covered by the NVICA have been allowed to stay in state courts.

The VICP now has >2500 claims, >75% alleging thimerosal injury. Due to these numbers, an "Autism General Order" of July 2002 established an a omnibus autism proceeding. This allows the claimants to file a short form with their name and basic information to allow the court to begin discovery of all the research around thimerosal and thimerosal injury. An evidentiary hearing will probably begin in spring 2004, and is hoped to be completed by July 2004. The U.K. has a similar omnibus activity, that addresses MMR and autism, that may also be decided early next year. The U.S. decision reached will then be applied to the individual cases. Petitioners can opt-in or -out of the proceeding, or leave after a 240 day deadline, and seek remedies in the tort system.

Portions (Sections 1714-1717) of the Homeland Security Act of 2002 attempted to incorporate some of the Frist VICP bill which would put these cases back into the VICP. It clarified the definition of vaccine-related injury or death, manufacturer, and defined "vaccine;" and extended coverage of the Act to thimerosal manufacturers. It would have applied to all pending civil actions, but the consolidated Appropriations Resolution of 2003 repealed those sections. Sen. Frist has reintroduced them in new legislation, Senate Bill 754 (S754), the Improved Vaccine Affordability and Availability Act. However, Dr. Evans was not certain that consensus could be achieved to pass that.

NIP. Dr. Melinda Wharton reported.

- The IOM Vaccine Financing Report is expected to be released this year. It addresses the roles and responsibilities of public and private agencies and providers for vaccine purchase and administration; the current levels of need for vaccines for persons without health plan coverage or with large deductibles or co-pay, reducing the time lag from recommendation to implementation; and future vaccine prices.
- The 56th World Health Assembly met recently and passed two resolutions: 1) to prevent and control influenza pandemics and annual epidemics, it urged the development of strategies to increase vaccination coverage of the elderly to increase coverage of the elderly to 50% by 2006 and to 75% by 2010; and 2) to reduce global measles mortality, it urged financial support for and full implementation of the WHO-UNICEF strategic plan for measles mortality reduction 2001-2005, so as by 2005 to reduce measles deaths to half of 1999 level (875,000 deaths).
- Wild polio virus from May 2002 to May 2003 were summarized. Progress in eradication continues, but the largest problems remain in India, Pakistan, and Nigeria. Control work there continues.
- Dr. Wharton thanked the AMA for its leadership in convening the National Influenza Summit in June 3, 2003. Its many participants include consumers and the private sector. Challenges identified included: 1) increasing vaccine demand/uptake (e.g, through enhanced communications efforts, extended vaccination campaigns, increased delivery system capacity) and 2) increasing the vaccine supply (e.g, by maximizing existing production capacity, bringing new manufacturers to the market, and employing new or improved vaccine production technology). These were communicated to the ACIP in a letter to Dr. Modlin.

With no further comment, the meeting adjourned at 3:30 p.m.

I hereby confirm that these minutes are accurate to the best of my knowledge.

John F. Modlin, MD, Chair

Date

Attendance

ACIP members present were:

Guthrie S. Birkhead, MD, MPH
Dennis A. Brooks, MD, MPH
Jaime DeSeda-Tous, MD
Reginald Finger, MD, MPH
Janet R. Gilsdorf, MD
Celine I. Hanson, MD
Myron J. Levin, MD
Gregory A. Poland, MD
Lucy S. Tompkins, MD, PhD
Richard Zimmerman, MD

ACIP members absent were: Judith Campbell, MD, John Salamone

Centers for Disease Control and Prevention Representatives

Alison Mawle, MD, NCID
John Livengood, MD, Acting Executive Secretary
Walter Orenstein, MD, NIP
Dixie Snyder, MD (ACIP Executive Secretary)
Melinda Wharton, MD, NIP

Ex-Officio Representatives

James Cheek, Indian Health Services (IHS)
Benjamin Diniega, Department of Defense (DOD)
Geoffrey Evans, National Vaccine Injury Compensation Program (NVICP)
Ben Schwartz, for Bruce Gellin, Director, National Vaccine Program Office (NVPO)
Randolph Graydon, Centers for Medicare and Medicaid Services (CMS)
Carole Heilman, National Institutes of Health (NIH),National Institute for Allergy and Infectious Diseases (NIAID)
Norman Baylor, for Karen Midthun Food and Drug Administration (FDA)
Kristin Nichol, Department of Veterans' Affairs (DVA)

Liaison Representatives

Jon Abramson, MD, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Carol Baker, MD, American Academy of Pediatrics (AAP)
Richard D. Clover, MD, American Academy of Family Practitioners (AAFP)
Stephan Foster, Pharm.D., American Pharmacists Association
Stanley Gall, MD, American College of Obstetrics and Gynecology (ACOG)
Peter Paradiso, for Geno Germano, Pharmaceutical Research and Manufacturers of America (PHARMA)
J. Henry Hershey, MD, MPH, National Association of County and City Health Officers (NACCHO)
Jose Ignacio Santos, for Carlos Santos, National Immunization Council and Child Health Program, Mexico
Rudolph E. Jackson, MD, National Medical Association
Samuel Katz, Infectious Disease Society of America (IDSA)
Monica Naus, MD, Canadian National Advisory Committee on Immunization
David A. Neumann, PhD, National Coalition for Adult Immunization (NCAI)
Kathleen Neuzil, American College of Physicians (ACP)
David Salisbury, London Department of Health
Robert Scalettar, American Association of Health Plans (AAHP)
William Schaffner, Infectious Disease Society of America (IDSA) and Guide for Adult Immunization
Jane Siegel, Hospital Infections Control and Prevention Advisory Committee (HICPAC)
Litjen Tan, PhD., American Medical Association (AMA)
James Turner, MD, American College Health Association (ACHA)

Representatives of the Centers for Disease Control and Prevention
Alison Mawle, MD, NCID
Allyn Nakashima, NCHSTP
Walter Orenstein, MD, NIP
Dixie Snyder, MD (ACIP Executive Secretary)
Melinda Wharton, MD, NIP

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Jody H. Hershey, National Association of County and City Health Officers (NACCHO)
Jose Ignacio Santos, National Immunization Council and Child Health Program, Mexico
Rudolph E. Jackson, National Medical Association
Samuel Katz, Infectious Disease Society of America (IDSA)
Martin Mahoney, AAFP

W. Paul McKinney, Association of Teachers of Preventive Medicine (ATPM)
Monica Naus, Canadian National Advisory Committee on Immunization
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James Turner, MD, American College Health Association (ACHA)

Agency Staff

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Agency for Toxic Substances and Disease Registry (ATSDR):

Centers for Disease Control and Prevention (CDC)

National Center for Birth Defects and Developmental Disorders (NCBDDD): Jennita Reefhuis

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP):

National Center for Infectious Diseases (NCID)

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Richard Besser	Yulia Desheva	Erin Murray
Achal Bhatt	Roz Dewart	Audrey Rekstin
Craig Borkowf	Cindy Dougherty	Tomoki Saito
Caroline Bridges	Keiji Fukuda	Pamela Srivastana
Lynette Brammer	Scott Harper	Tim Uyeki
Maria Cano	Alan Janssen	Teri Wallis
Joanne Cono	Ann Moen	Cynthia Whitney

National Immunization Program (NIP):

James Andrews	Nancy Fasano	Gina Mootrey
Francisco Auerhoff	Julie Gilchrist	Pedro Moro
Carolyn Bachino	Sharon Greene	Joe Mulinare
Barbara Bardenheier	Penina Haber	Arnulfo Muralles
Roger Bernier	Beth Hibbs	Trudy Murphy
Kris Bisgard	Marika Iwane	Huong Nguyen
Roumiana S. Boneva	Allison Kennedy	Glen Nowak
Karen Broder	Andrew Kroger	Diane Z-Ochoa
Scott Campbell	Laurie A. Johnson	Carolyn O'Mara
Louisa Chapman	Deva R. Joseph	Bette Pollard
Bob Chen	Herschel Lawson	Susan Reef
Steve Cochi	Charles LeBaron	Lance Rodewald
Maggie Coleman	Nancy Levine	Marty Roper
Margaret Cortese	Dean Mason	Tammy Santibanez
Edward Eduardo	Mehran Massoudi	Jean Santoli
Gary Euler	Elaine Miller	Kari Sapsis

Rich Schieber
Ben Schwartz
Judy Schmidt
Jane Seward
Sean Shadomy
Jim Singleton
Shannon Stokley
Ray Strikas
Charlie Thompson
Amra Uzicanin
Greg Wallace
Sabrina Walton
Donna Weaver
Bruce Weniger
Skip Wolfe
Jane Zucker

Office of the CDC Director: Larry Pickering

Department of Defense (DOD): John D. Grabenstein

Department of Homeland Security (DHS): *Federal Emergency Management Agency (FEMA):* Elaine Chan

Food and Drug Administration (FDA): ChrisAnna Mink, Dorothy Scott

National Institutes of Health (NIH): *NIAID:* Barbara Mulach; Polly Sager

Members of the public or presenters to the committee in attendance were:
Katherine Aquino, New Yor State Department of Health, Albany, NY
Kate Arnohl, GDPH, Atlanta, GA
Joe Beaver, TN Department of Health
Robert B. Belshe, St. Louis, MO
Joan Benson, Merck & Co., Inc.
Sop[hie Biernaux, GSK, Rixensart, Belgium
Paul Blum, Acambis
Damian Braga, Aventis Pasteur
Adnan Bott, JP Morgan, NY, NY
Dominique Boutraiu, GSK, Belgium
Andrew Bowser, freelance medical writer, Brooklyn, NY
Lynn Bozof, National Meningitis Foundation (NMF)
Eddy Bresnitz, New Jersey Health and Senior Services, Trenton, NJ
Kelly Bruce, GA Immunization Program
Margart Burgess, NCIRS, Australia
Kim Bush
Pat Cannon, Wyeth, Newnan, GA
Iksung Cho, MedImmune Vaccines
Kathleen Coelingh, MedImmune Vaccines
Chris Cohen, GlaxoSmithKline (GSK)
Kevin Colley, Maxim Health Systems, Winter Park, FL
Ed Connor, MedImmune
Lenore Cooney, Cooney/Waters, New York, NY
Louise Z. Cooper, MD, Nnii
Julia Cordova, MedImune
Linda D'Antonio, DCI, Inc., E. Syracuse, NY
Dack Dalrymple, Dalrymple & Associates/Pink Sheet, Washington, D.C.
Michael Decker, Aventis Pasteur/Vanderbilt University
Cathy Dunn, Nashville, TN
Kris Ehresmann, Minnesota Department of Health, Minneapolis, MN
Joseph Eiden, Biologics Consulting Group, Danville, CA
Steven Foster, American Pharmaceutical Association

Betsy Frazer, AQAF, Vestavia Hills, AL
Mary Gadek, Aventis Pasteur
Matt Garrett, Wyeth
Diana Gaskins, GA Immunization Program, Atlanta, GA
Kristine Gebbie, Columbia University, NY
W. Paul Glezen, Gaylor College of Medicine
Jesse Greene, South Carolina Department of Health and Environmental Control
Robert Grenwelge, Houston Department of Health and Human Services, Houston, TX
Neal Halsey, Johns Hopkins University, Baltimore, MD
MD. Hamlin, Keystone Center, Keystone, CO
Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Alicia Haupt, Philadelphia Department of Public Health
Richard A. Haupt, Merck Vaccine Division
Bill Hausdorff, Rochester, NY
Kimberley Hazelwood, GA State Public Health
Colin Hessel, MedImmune Vaccines
Kenneth Holiness, Department of Human Resources (DHR), Atlanta, GA
Philip Hosbach, Aventis Pasteur
Barbara Howe, GSK
Melonie Jackson, Georgia Chapter, AAP
Mike Kepferle, NMA
Peter Khoury, Baxter BioScience
Sue and Al Koenig, Coatesville, PA
Heather Kotler, GA DHR
Dr. J. Michael Lane, ORISE, Oak Ridge, TN
Jim Lathrop, PowderJect Vaccines
Ira Longini, Emory University
Harold W. Lupton, Aventis Pasteur
Marie-Michele Leger, American Academy of Physician Assistants, Alexandria, VA
Jeff Levine, Ketchum, Washington, D.C.
Anita Manning, USA Today, Wilmington, DL
Michele Marill, Hospital Employee Health, Decatur, GA
Michael Mattiol, Aventis Pasteur
Donald G. McNeil, Jr., New York Times
Paul Mendelman, MedImmune
Marie Murray, Recorder, Atlanta, GA
Martin Myers, UTMB, Galveston, TX
John M. Neff, University of Washington, Seattle, WA
Paul A. Offit, Children's Hospital of Philadelphia
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Peter Paradiso, Wyeth Vaccine, West Henrietta, NY
Andrea Pernack, IOM
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Jill Pulley, MedImmune
James Ransom, National Association of City and County Health Officers (NACCHO)
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Fred Rutson, Aventis Pasteur
Catherine Shaichet, Atlanta Journal-Constitution
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Scott Thuler, PosderJect Vaccines
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Miriam E. Tucker, Pediatic News/Family Practice News, Rockville, MD
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Robert Walker, MedImmune
Martin Wasserman, GSK
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Matthew Williams, Flu Central, Doraville, GA
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